UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

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46th MEETING

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MONDAY, JULY 14, 1997

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BETHESDA, MARYLAND

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The Advisory Committee met in the Versailles Room of the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:30 a.m., Joseph McGuire, Jr., M.D., Chair, presiding.

PRESENT:

JOSEPH McGUIRE, Jr., M.D.	Chair
SUSAN COHEN, B.S.	Member
LYNN M. DRAKE, M.D.	Member
KEN HASHIMOTO, M.D.	Member
JOEL MINDEL, M.D.	Member
E. WILLIAM ROSENBERG, M.D.	Member
EDUARDO TSCHEN, M.D.	Member
M. ROY WILSON, M.D.	Member
TRACY RILEY	Executive Secretary

GOVERNMENT EMPLOYEES, CONSULTANTS, AND GUESTS :

WILMA F. BERGFELD, M.D.
LAWRENCE B. HARKLESS, D.P.M.
PHILIP T. LAVIN, Ph.D.
BENJAMIN A. LIPSKY, M.D.
DAVID J. MARGOLIS, M.D.
CLINTON M. MILLER III, Ph.D.
O. FRED MILLER III, M.D.
THOMAS A. MUSTOE, M.D., Ph.D.
EVA F. SIMMONS-O'BRIEN, M.D.
DAVID R. THOMAS, M.D.

ALSO PRESENT :

JACQUELINE A. COELLN, R.Ph.
WILLIAM H. EAGLSTEIN, M.D.
DAVID FINBLOOM, M.D.
JOHN JOHNSON
LIBERO MARZELLA, M.D., Ph.D.
BARBARA PERRY, Ph.D.
MARTIN C. ROBSON, M.D.
ALLAN SAMPSON, Ph.D.
BASANT SHARMA, Ph.D.
JANICE M. SMIELL, M.D.
DAVID L. STEED, M.D.
KURT STROMBERG, M.D.
KAREN WEISS, M.D.

A G E N D A

P R O C E E D I N G S

(8:40 a.m.)

MR. McGUIRE: Good morning. Good morning. The meeting is in order. If people can be seated, the meeting is in order.

Those of you who think you're in a non-prescriptive room or in the wrong room, if you see -- if you go down there and you see some people who you think they ought to be in this room, tell them that we're meeting.

This is the forty-sixth meeting of the Dermatological and Ophthalmic Drugs Advisory Committee meeting. My name is Joe McGuire.

We have a -- we have a long day and a lot of complex things to consider. The sponsor is presenting many years of work with PDGF and its efficacy and safety in diabetic -- in diabetic ulcers.

I'd like to introduce Tracy Riley, who's the executive secretary of the committee, who will read a conflict of interest statement.

MS. RILEY: Good morning. Welcome to the forty-sixth meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee.

I will read the following conflict of

interest statement:

"The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

"Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for the appearance of a conflict of interest at this meeting, with the following exception:

"In accordance with 18 U.S. Code 208(b)(3), full waivers have been granted to Dr. Joseph McGuire, Dr. Lynn Drake, Mrs. Susan Cohen, Dr. Joel Mindel, Dr. E. William Rosenberg, Dr. Thomas Mustoe, and Dr. Philip Lavin.

"In addition, limited waivers have been granted to Dr. Lawrence Harkless and Dr. Benjamin Lipsky. Under the terms of these limited waivers, Dr. Harkless and Dr. Lipsky will be permitted to participate in the Committee's discussions concerning Regranex. They will,

however, be excluded from any vote related to this product.

"A copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

"In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

"With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon."

Also, the Committee has invited the following consultants to participate in today's meeting as temporary voting members:

Dr. Wilma Bergfeld;

Dr. Fred Miller;

Dr. Eva Simmons-O'Brien;

Dr. Philip Lavin;

Dr. David Margolis;

Dr. Clinton Miller;

Dr. Thomas Mustoe; and

Dr. David Thomas.

In addition, the Committee has invited the following non-voting consultants and guests to participate in the meeting:

Dr. Diane Cooper;

Dr. Lawrence Harkless; and

Dr. Benjamin Lipsky.

I do not believe that Dr. Cooper will be participating today, but she will tomorrow.

MR. McGUIRE: This is a rather larger table than usual, and we have a number of consultants. What I'd like to do is to start at my far right and have each of you introduce yourselves and just name your institution.

MR. FINBLOOM: Dr. David Finbloom, Director of the Division of Cytokine Biology.

MR. MARZELLA: Dr. Louis Marzella from the Department of Clinical Trials at FDA.

MS. WEISS: Dr. Karen Weiss, Director of Division of Clinical Trials, FDA.

MR. STROMBERG: I'm Kurt Stromberg, Division of Cytokine Biology, FDA.

MR. THOMAS: David Thomas, Geriatric

Division, University of Alabama at Birmingham.

MR. MUSTOE: I'm Thomas Mustoe, Northwestern University Medical School, Chicago.

MR. HASHIMOTO: I'm Ken Hashimoto, Department of Dermatology, Wayne State University in Detroit.

MR. C. MILLER: Dr. Clint Miller. As of four months ago, I was not institutionalized.

(Laughter.)

MR. F. MILLER: Dr. Fred Miller, the Geisinger Division of the Penn State/Geisinger Health System in Pennsylvania.

MS. DRAKE: Dr. Lynn Drake, Department of Dermatology, University of Oklahoma Health Sciences Center.

MR. McGUIRE: Joel McGuire, Stanford University, Dermatology.

MS. BERGFELD: I'm Wilma Bergfeld, Departments of Dermatology and Pathology, Cleveland Clinic Foundation.

MR. ROSENBERG: E. William Rosenberg, Dermatology and Preventive Medicine, University of Tennessee, College of Medicine.

MR. MINDEL: Joel Mindel, Departments of Ophthalmology and Pharmacology, Mt. Sinai Medical

center.

MR. LAVIN: Philip Lavin, Boston Biostatistics and Harvard Medical School.

MR. MARGOLIS: I'm David Margolis, Departments of Dermatology and Biostatistics and Epidemiology, University of Pennsylvania.

MR. TSCHEN: Dr. Eduardo Tschen, University of New Mexico.

MR. HARKLESS: I'm Lawrence Harkless, Department of Orthopedics, Division of Podiatry, UT Health Science Center, San Antonio.

MR. LIPSKY: I'm Benjamin Lipsky, University of Washington, Department of Medicine, and in Seattle, the Antibiotic Research Committee.

MR. WILSON: M. Roy Wilson, UCLA, and Charles Drew University.

MR. McGUIRE: Thank you.

We will start by hearing from the American Diabetes Association.

Are you going to read the statement or are they giving it?

MS. RILEY: I'll read it, if you like.

MR. McGUIRE: Okay. Ms. Riley will read the statement.

STATEMENT: AMERICAN DIABETES ASSOCIATION

MS. RILEY: "We are writing on behalf of the American Diabetes Association to provide information to the Food and Drug Administration's Dermatologic and Ophthalmic Drugs Advisory Committee, to review the safety and effectiveness of becaplermin for the treatment of diabetic foot ulcers.

"In the United States there are currently 16 million people with diabetes, a serious and devastating disease, with over 600,000 new cases diagnosed each year. Diabetic foot ulcers, as well as other foot problems, represent a major cause for diminished quality of life and diminished productivity for individuals with diabetes. Foot ulcers are common, and affect approximately 15 percent of all people with diabetes during their lifetimes. But ulcers and lower limb conditions also represent a major drain on the health care system, as a 1986 study estimated that foot ulcers alone account for at least $150 million of the direct costs attributed to Type 2 diabetes.

"No mention of diabetic foot ulcers would be complete without discussing their role in patients' future risk of lower extremity amputation.

The National Health Discharge Survey shows that such foot ulcers precede nearly 85 percent of amputations. With 54,000 diabetes patients undergoing such lower extremity amputations each year, human suffering is immense.

"What's more, with reimbursement costs for such amputations, estimated at between 11,000 and 27,000 dollars per event, significant health care dollars, between 600 million and 1.5 billion, are expended each year.

"The American Diabetes Association believes that new therapies to treat diabetic foot ulcers are necessary to improve the lives of the people with diabetes.

"We understand that becaplermin works to improve the healing process after foot ulcers are discovered and undergo debridement. If this topical treatment is shown to be safe and effective, we believe that its use will facilitate improved care and treatment, thereby helping to reduce an enormous personal and societal burden caused by lower limb complications.

"The American Diabetes Association applauds the scientific and medical research community and the FDA for the development, review,

and clearance for marketing of new medications that can safety and effectively treat diabetes and its complications. We believe that safe and effective treatments, as determined by rigorous FDA review, are needed by health care professionals who treat people with diabetes.

"If any additional information on diabetes or foot complications is needed, we would be happy to provide it for your consideration."

And it's signed by Steven J. Sazzalino, the chairman of the board; Mayer B. Davison, M.D., the president, and Christine A. Beebe, president for health care and education.

MR. McGUIRE: Are there other statements for the open public hearing?

In that case, let's go -- let's move right ahead with the scientific presentation. Dr. David Finbloom will begin.

In the interest of saving time, each speaker from the Agency will introduce the next speaker.

PRESENTATION BY DAVID FINBLOOM, M.D.

MR. FINBLOOM: Good morning.

In today's Dermatologic and Ophthalmic Drug Advisory Committee meeting we'll be

hearing presentations by both the sponsor and the Center for Biologics Evaluation and Research, of a product used for the treatment of chronic diabetic ulcers.

The product is called Regranex, and represents an aqueous gel that is formulated with buffered sodium carboxymethylcellulose as the gel vehicle, into which the active drug substance, becaplermin, at 0.01 percent, is mixed.

Becaplermin is the BB-isoform of the human platelet-derived growth factor -- human platelet-derived growth factor whose biologic properties will be discussed later by Dr. Stromberg. Becaplermin represents the first application for licensure of a recombinant DNA-derived growth factor that the Center for Biologics is reviewing for use in the treatment of chronic cutaneous ulcers.

Both the Center for Drugs and Biologics Evaluation and Research have licensed several recombinant DNA- derived products over the last ten years. These have included products such as growth hormone, insulin, interferons of all three classes, interleukins, enzymes, and specific growth factors such as erythropoietin, and granulocyte colony stimulating factor.

The application for a biologic product is referred to as the biologic license application, and abbreviated BLA. Although the applications are approaching a seamless process between the Centers, the actual review of the application itself remains somewhat unique for each Center.

The Center for Biologics is composed of divisions that employ scientists that both review license applications and carry out laboratory-based research. Most of these scientists carry out research on the classes of products they review. These scientist-reviewers are responsible for most of the product reviews within the Center, and consist of molecular biologists, cellular biologists, microbiologists, biochemists, immunologists, and others.

The clinical portion of the license application is reviewed by a clinicians who, in the Office of Therapeutics, are located within the Division of Clinical Trial Design and Analysis. Many other individuals actually take part in the review of the BLA, and they too will be mentioned later by Dr. Stromberg.

The use of growth factors as

promoters for wound healing has been an area of study for many years with investigators and sponsors both at the preclinical and clinical levels of investigation.

At this time I would like to turn over the podium to Dr. Mustoe. Dr. Mustoe, who has experience both at the bench and at the bedside on the use of PDGF in pressure ulcers, will discuss the role of growth factors in wound healing.

Thank you.

GROWTH FACTORS IN WOUND HEALING

THOMAS A. MUSTOE, M.D., Ph.D.

MR. MUSTOE: Maybe I'd better make sure that you can hear me.

Kurt Stromberg asked me to modify some comments I had made at the Wound Healing Society. And what I really wanted to do today is, first of all, set the stage. I think there's ample evidence that multiple growth factors do have an impact on various aspects of wound healing in animal studies. And I think that we've been doing animal work now for about ten years. This is the first time that we're here. And I guess one of the real issues is, why has it taken so long?

I think chronic wounds are clearly a

very, very complicated system, and I'd like to focus my comments today on some issues that I think are relevant, that must be considered, and I think are relevant to the diabetic ulcer trials that we're going to be looking at today.

Diabetic ulcers are one of the three main groups of chronic wounds, others being venous leg ulcers and pressure sores. And we know that classical information on chronic wounds -- and this is really historic, but some of it is actually only about twenty-five years old -- is that occluding a wound, moist wound healing, will speed up epithelialization. Secondly, that debridement is beneficial. Interestingly, there's a dearth of actually well-controlled prospective studies to that, but I think this is a clinical aphorism that everyone accepts. And infection delays healing -- classic studies by Marty Robson and Tom Krizek, that skin grafts will not take if a wound has greater than 105 bacteria per cc. And this has been -- certainly can carry on over into chronic wounds.

Clinical observations are -- we know that most chronic wounds do respond to standard management. And I would say that certainly in terms of venous ulcers and diabetic ulcers, standard --

optimal standard therapy will heal 60 to 70 percent of wounds.

What is optimal standard therapy? Well, it can involve a variety of dressings. And we're to hear in the next -- specifically relating to diabetic ulcers, the next talk. But certainly debridement, meticulous and frequent, absolutely keeping the wound clean of exudate and necrotic tissue, edema control, and pressure relief are the -- as well as moist healing, are what are going to achieve healing in 60 to 70 percent of patients.

However, there are patients who are resistant to healing. This woman has had this venous ulcer now for -- when I last saw her, for about forty years. She had not -- had tried multiple, multiple therapies. The wound hadn't changed very much. She was kind of in symbiosis with it.

The question is what -- and I think it's one that's received increasing attention: what is it about chronic wounds that makes them chronic? Is there something unique? Is there some mechanistic issue that really is the key to chronic wounds? Or -- and I think this is what I'd like to explore today: I think it's really a combination of

factors which in aggregate can make a profound difference.

First of all, I think that chronic wounds are really predominantly a problem in the aged. In multiple studies, if you exclude paraplegics, pressure sores groups are an average of sixty to seventy years old. I think you'll see the diabetic ulcer patients today are -- even though diabetes occurred at an early age, the age is older rather than younger. And venous ulcers also, in several studies, are in the age group of sixty to seventy years old. I think it's an area that's frequently overlooked.

What is the impact of aging? Well, I think that there are lots of things going on. But one of the clearest issues, areas where we see the impact of aging, is if we look at the survival rate from a 50 percent total body burn. Between the ages of twenty -- and this is probably really the age of ten -- to the age of about forty to fifty, the survival rate changes very little, and this is just taking all comers. However, by the time you get to sixty, seventy years old, there's a steep falloff in survival. And so I think by the age of seventy, the survival is much less than 50 percent.

What's going on in the burn? Obviously, lots and lots of things. But I think it has some relevance when we think about chronic wounds which -- basically, the aged have a much more difficult time dealing with the -- with the impact of stress. And a chronic wound, I would -- I would say, is a stressed environment.

Now, one area of animals that bears this out is -- we've spent an awful lot of time looking at this rabbit ear model, in which we make 6-millimeter wounds on the back of an ear. The nice thing is that the anatomy is fairly constant, so you can make the wound -- the ear is also reproducibly ischemic. You'll still get complete healing, because these wounds don't contract, because the cartilage splints them. It's very easy to quantify both the granulation tissue and epithelialization. And this just shows that the blood supply is very reproducible, so we can make these wounds reproducibly ischemic by dividing two of the three major vessels in the dermal circulation.

Now, if we look at an incision in this model, we first of all look at -- if you look on the -- in a young animal, and you compare non-ischemic wounds to an aged animal, there is -- and

this is -- an aged animal is about the equivalent of about a forty-, fifty-year-old patient. There is a decrement in breaking strength over time. However, ischemia, and it's not surprising, is a marked impairment of wound healing. However, if you combine ischemia and aging, the bottom really drops out. And I -- we have seen this now in several -- in different -- three different animals, that there really is at least an additive effect of the impairment of aging and ischemia on wound healing.

If you look at, in a dermal ulcer model, granulation tissue, and if you took a young six month old rabbit, again ischemia has a profound impairment on healing. But this is about a day-ten animal. By the time you get out to a thirty-month-old, which is still a relatively young animal, the wound healing -- there's essentially no healing at this time point. And so again we see a pretty profound impairment of this interaction between aging and ischemia.

Finally, in a model where we make the rabbit ears repeatedly ischemic -- in other words, the dermal circulation tends to restore, and by repeatedly interrupting the dermal circulation, we get a model where you have chronic ischemia. And

this ischemia is not as profound as you might think. The TCPO2, if you will, of tissue, goes from about 45 down to about 28. And in this model, at twenty-six days there's still essentially no healing at all in this model, in the aged situation. In a young animal in this model, you get complete healing at this time point.

I think that another issue as well as age -- and I've been obviously focusing on ischemia -- I think is a critical issue in every chronic wound. Certainly every chronic wound model -- every chronic wound has ischemia reperfusion as part of the process. In any -- in any wound that is chronically -- any chronic wound is going to have a fair amount of scar tissue in the local environment, I think. The local microenvironment is ischemic. But in addition, there have been some recent evidence -- proposals that venous ulcers are -- in fact, have ischemic reperfusion injuries. Certainly in pressure sores and diabetics that's very true.

I think in terms of thinking about the future, we tend to -- in the past have through about oxygen as a fairly inert molecule that is -- it is certainly important for oxydative phosphorylation and the key to life, but is -- and

we really haven't thought about it as a signal transducer. But I think there's increasing evidence that oxygen is a signaling molecule that can certainly help regulate erythropoiea in kidneys, is -- in multiple models has a major effect on VEGF, in vitro does help regulate PDGF in endothelial cells, has been shown to help regulate PDGF-beta in fibroblasts. And I think what brings it together is that recently, in the last couple of years there's been sequenced a nuclear transcription factor, hypoxia inducible factor, which is present in a wide number of cells and is undoubtedly involved in signal transduction pathways that may very well secondarily interact with growth factors.

Now, what else is going on in chronic wounds?

This is a wound that is -- looks to be well perfused. It certainly has healthy granulation tissue, but it quite clearly has -- it's easy to believe has a high bacteria count. And the issue is that unless a wound is cellulitic and the surrounding tissue is -- obviously has high numbers of bacteria, it's very difficult visually, unless you get a severe situation, I guess, to see what is the -- what are the number of bacteria in a wound.

Where this is relevant -- and I'm going to go back to that slide. But I think it's that there's been multiple studies in the last couple of years that have shown that there's significant numbers of increased proteases from wounds, in chronic wounds. There's also decreased growth factors and increased growth factor inhibitors. What's interesting is that the proteases are generated from polys. And I would propose that the primary issue, why do you see increased proteases in chronic wounds, it's because of the level of bacteria in a wound. And I think this is a controllable issue.

We have looked at an interesting cotheption-G mouse knockout. And I think that the cotheption-G is an enzyme protease that's found in polys. The interesting thing about the model is that -- is that the -- phenotypically, these animals are absolutely normal. They do have normal circulating levels of polys.

But what's interesting is that we -- if we go to a wound situation, there are a significant number of increased polys, by a mechanism that I won't go into. But although it's been chronically -- it's been -- the classical

literature has been that if you -- polys don't have a significant impact on breaking strength.

We see in this model that at a time when there are increased numbers of polys in the wounds, which are by day seven, eight, nine, in fact breaking strength is significantly decreased. However, by day ten or twelve in this model, the number of polys in this model have returned to normal, and breaking strength returns to normal. So I would say that, in fact, increased numbers of polys -- and that's sort of -- it's not clinical, intuitively it's true are bad for wounds.

In addition, if you go back to this situation, it's -- what about the ability of polys to be effective in a chronic wound? Polys kill bacteria with superoxides. And in work by Tom Hunt and others, it's been found that in order for polys to work effectively, you really need a PO2 of 25 to effectively generate superoxides. The wound microenvironment classically has a low PO2. In a chronic wound, it's got to be a very low PO2.

And so if we go to our situation of a diabetic ulcer, I think you're going to hear the tremendous importance of debridement on treating a diabetic ulcer. I think that one issue is that --

are you converting a chronic wound into an acute wound? And I think that is -- and there's -- is there some proliferative block?

I think another issue is, you can say you're converting a poorly perfused wound into a well perfused wound. We know that in that situation you -- it may be the real key to why it's so beneficial.

Now, how does this all relate to PDGF?

There have been multiple strategies on how to promote wound healing. Growth -- multiple growth factors have been tried. I think one common theme is that macrophage activation is important, and I think that is a key mechanism of why PDGF works. I think increasingly we're recognizing that the matrix is very important, and that in a chronic wounds the problem may not be an impairment of epithelial proliferation, but it is more an impairment of epithelial migration. Organizing the matrix may be essential. And this is presumably also how PDGF is having an effect.

I first got my start in wound healing working with Tom Duel and then with Glen Pierce at Washington University in St. Louis. Tom Duel was --

first made the correlation between -- that PDGF was a proto-oncogene in C-cysts. We looked back in 1987 in our rat incisional model at PDGF, and found that it did in fact increase breaking strength. And this is -- I've been looking at PDGF for a long time.

What's interesting about it is that PDGF, one dose times zero -- and this is only up to twenty-one days, but you see an increase in breaking strength out to forty-nine days. And I think that one of the unique properties of PDGF versus other growth factors is this tremendous cascade effect it must induce. Because it's still remarkable to me that a single additive at day zero could result in an increased breaking strength at day forty-nine. And I think this is -- certainly compared to other growth factors we've looked at, is relatively unique.

If we look at PDGF in a rabbit ear model, again it's primary impact is increasing granulation tissue. And routinely, we predictably see a 100 percent increase in granulation tissue at seven days.

I would just say also that we -- if we look at impaired models, PDGF works well in the ischemic model. It works -- its effects are even

more well seen in an impaired model of aging and ischemia. So there's lots of reasons to believe that PDGF may be effective in the chronic wounds environment, which is going to be an aged, ischemic environment.

Interestingly, its effects on -- this was a study that was -- the lead author was Glen Pierce -- that I participated in. This is a rabbit ear model, leading edge of a wound. And control -- this is a Sirius red stain, and is for collagen. And you see that TGF-beta has a very dramatic induction of collagen. PDGF -- this is all wound; you see virtually very little collagen. But what you do see, and this is an Alcian blue stain for glycosaminoglycan, that PDGF's provisional matrix initially is primarily glycosaminoglycan, versus TGF-beta which has -- is predominantly collagen. So I think you can see that TGF-beta does -- I mean, PDGF-beta does have significant effects, effects on the matrix.

I'd just close by saying that in terms of future needs for research, I think it's clear that a single growth factor is going to -- you're going to get a tyrosine-kinase receptor transduction pathway. But there are multiple

pathways now that probably are important in wound healing, pathways mediated through integrants, pathways mediated through chemokines, pathways -- and we've certainly focused on hypoxia, oxygen, other stress signals. And we may be -- the key to further improvements in healing may be to try to actively look at the -- stimulating healing by exploring more than one single transduction pathway at once.

Thank you very much.

I guess the next speaker is Dr. Miller, who is going to talk about standard therapy in diabetic ulcers. I am going to let him introduce himself in terms of his eminent qualifications for this talk. Thanks.

STANDARD THERAPY IN DIABETIC ULCERS

O. FRED MILLER III, M.D.

MR. F. MILLER: My name is Fred Miller from Geisinger. And I'm going to talk about the standards in care that we've encountered and I think that you read in the literature. And these are standards of care for the diabetic foot ulcer, specifically neuropathic ulcers. I'll begin with conclusions. There are four essential steps in the treatment of ulcers.

The first thing is, you must assess the vasculature to determine, is this ischemic or is it neuropathic? Because the approaches are totally different. If there is ischemia, then that patient has to be referred for vascular studies and possible vascular reconstruction.

In the neuropathic ulcers, it's imperative to debride devitalized tissue and also the callosities, and then in your therapy to relieve all pressure and friction from the site. And that is more easily said, many times, than accomplished.

We also do baseline X-rays just to assess the bone and the soft tissue. Okay.

So in the assessment, is it a neuropathic ulcer, or is it an ischemic ulcer?

The ulcers, interestingly, in the diabetic foot will be either predominantly ischemic or neuropathic. We do see patients who have severe ischemia and neuropathy, but those ulcers will manifest as ischemic ulcers, and the treatment will be for the ischemia.

Let's begin very briefly with the ischemic ulcer. And I will show you clinical cases.

This is a gentleman who had excruciating pain with this ischemic ulcer. You can

see the livido-like changes around this ulcer. The foot was cool, the pulses were diminished, he had abnormal vascular studies. He was revascularized, and here he is just a couple of weeks after revascularization. The pain from the ulcer is gone in the recovery room if the revascularization is successful.

So the first thing, then, is to assess the person for any ischemic component.

This is a gentleman with his foot hanging over the bed; we're looking up at it. And he has the dependent rubor of ischemia. Again, the foot is cool, the pulses are diminished. These patients are evaluated primarily with ABIs followed by photo-plethysmography, and then they will go on to angiography and surgery, if possible. These same patients, if you elevate the feet and press on the tissue, you can see you get blanching. They get delayed filling of their foot, then, with dependency. So this is the ischemic ulcer. These are not the ulcers that we're discussing today.

What about the neuropathic ulcers? What do these look like?

First thing is, you -- this is a warm foot. The pulses usually are bounding. If you look

at the configuration of this foot, it is misshapen. This is a Charcot foot, because the bones are awry. The ulcer itself is -- there's a deep ulcer with a rather large callus or pseudocallus around it. It can be malodorous just from the changes in the tissue and from the heavy callus. The malodor does not mean that it is infected. There is no evidence of cellulitis here. This foot is insensate; you can debride it without any local anesthesia.

Here's another one. When you debride these, you will have an iceberg phenomenon. The ulcer might look very small until you debride it, and when you've debrided it, it's much larger as you get rid of all the callus.

How does these ulcers form? It is predominantly pressure on abnormal points of pressure on the -- on the foot. They have bony changes in the feet, they have claw toes, they have hammer toes, they get slippage of the foot pads over the metatarsal heads, and many of them have Charcot feet. So it's this repetitive and friction on pressure points.

This was work that was done at Carville by Dr. Paul Brand. And he showed that if you have continuous pressure of one pound per square

inch for twelve hours on a bony prominence, you can have necrosis.

And these folks will often have ill-fitting shoes, because as their sensation begins to leave the feet, they will get shoes that really don't fit. You know, they'll get them very, very tight, just to get a little bit of feeling. And in fact what they're doing is, they're wearing shoes that don't fit, and they get pressure on these abnormal bony prominences.

The other thing that happens is, because of the lack of sensation, many times changes in vision, they step on objects or they have objects in their shoes which will damage the skin. And this is the most common source of ulceration, where they just repetitively walk on the same area without realizing that they're damaging the skin. They will have erythema, and then with repeated trauma they will get breakdown.

Paul Brand said that normal sensation protects us and whispers gently to make the unconscious change to a new position or altered gait. And they demonstrated this in runners. As they developed a little bit of erythema on the foot, they would automatically pronate or supinate to

avoid pressure. These folks with neuropathy do not have the sensation, and consequently they will just repeatedly go forward on the same area.

How do we test these folks? It's important that they be seated so that they can touch the area that you are testing. We use microfilaments, a 10-gram microfilament. You can also use a Q-tip.

And you can see in this young woman we're using a Q-tip, and she has an ulcer on the second metatarsal head. We're using the wooden part of this, of this Q-tip, and you can see I'm pressing on this site. And when she tells me she has feeling, do you see where she's putting her finger? It's important that -- again, that the patient be able to touch the area where he or she feels there is sensation, because the sensation is often displaced.

Now, many of these folks are completely neuropathic. Others will retain some sensation, but it is displaced and not protective, so that you can touch someone on the sole, and the person will touch the ankle or will say that he feels it on the ankle. If the person is lying down and you do this, you say, "Gee, sensation is

intact," when in fact it's displaced and not protective.

How do we approach the care of these ulcers? You know, what is the standard of care? It's very difficult, because there are many players. It's everyone from X-rays to orthopedics to infections disease to dermatology, depending upon your institution. And what you need is unanimous vision. But there are some basic principles to which we can adhere.

The first thing is, you have to have foot care in the diabetic. And this means very assiduously looking at the feet on a daily basis. They should be inspected, either by the patient him- or herself, or by an attendant if vision is a problem, or obesity or whatever might be the limiting factors.

If there is erythema or swelling, they should stay off the foot. And if this persists for a few hours, it should certainly be checked. Is this an early cellulitis? Is it a wound that is just beginning because of the tissue damage or compromise?

The neuropathic ulcers have a lot of callus, they have a lot of debris, and they must be

debrided. And the debridement has to be aggressive. And I mean really aggressive; you do this without anesthesia. They will bleed copiously, and all you do to stop the bleeding is, you lie on it until the bleeding stops. It is not a problem, ultimately stopping the bleeding. But the debridement has to be aggressive and it has to be complete. If you debride them completely, repeated debridement should not be necessary, other than trimming callus. And if you do reform callus, that's an indicator that you're getting pressure and friction, which you must avoid if you're going to heal these wounds.

We don't rely on proteolytic methods and wet-to-dry dressings in the debridement of neuropathic ulcers.

Look at the iceberg effect of this lesion. You can see it looks quite small. there's significant callus, there's pseudocallus around the wound. Here it is before debridement, and here it is after debridement. There's a considerable difference. But if you're going to heal this ulcer, you must get rid of that callus, because there's no way for new epithelium to come over that wound unless you get rid of all of that callus and then maintain a moist environment during the healing

process. And for the most part, you can do this with physiologic saline.

I'm going to show you a couple of cases. And these are the norm; we see these cases on a day to day basis.

Here's a woman with an ulcer on her toe, and it's being debrided aggressively. You can see the way I'm debriding it here. This was one of the patients whom I saw. And she had shard of bone in her toe, and this was felt to be an osteomyelitis. She was not treated with an antibiotic. She doesn't have a lot of cellulitic component here. And what I did was, with rongeurs and with curettes and with hematostats, picked out the bone. And that's a fragment of bone or pieces of bone that I'm taking out with the rongeur.

And here she was after the debridement was completed, and here she was a week later. And you can see I can still put a probe into the toe. And here she was seven weeks. I checked the dates on these patients.

And these are the norm; I'm not picking out patients who are extraordinary. These are the norm. This was a seven-week time to complete healing.

But the debridement had to be aggressive. When she came in, she had packing through her toe, but she had not been debrided adequately.

So it's important to remove pressure and friction from these sites. Weight-bearing -- you have to eliminate all the weight-bearing.

Here's a gentleman with an ulcer on the fifth metatarsal head. this was another eight weeks to complete healing. And you can see how difficult it is to remove the weight-bearing from this area, and in him we did contact casting. And contact casting in our hands is the norm for metatarsal head lesions, and also for heel lesions. Because as you watch the way you walk, they're the areas that really bear the brunt. You go off your heel and you're then off your metatarsal heads. So we use contact casting to distribute the weight after the areas have been debrided. Here he is before, and here he is seven weeks after contact casting.

We have modified the Carville technique. We begin with a Unaboot and then a plaster cast and then a fiberglass cast, and then we encourage walker, crutches, or cane support. But

most of the times patients don't really do that, they pound away on their -- on their cast. We change the cast at one week, and then it is reapplied. And it might be kept on for two, three, or even four weeks before we remove it again. But it's imperative, before you put the contact cast on, that the wound be adequately debrided and there's no infection in the foot. Here's the contact cast, and it will be changed in a week.

This was a gentleman who had this ulcer for ten months, and you can see how -- not necrotic, but the amount of debris and the amount of callus there. And here he is after eight weeks of contact casting. And here was the before. And look at the amount of callus there and debris in that wound. This has to be really aggressively debrided. And after aggressive debridement and contact casting, healing.

What do we do after the healing? This is really important, because when you look at the studies, what do they say? Thirty percent of these people have a recurrence of their ulcers. We have to get them into shoes. Sometimes it has to be extra-depth shoes, sometimes molded shoes. But many times we can get away with the walking or running

shoes.

If we used the running shoes, for example, we'll take out the insoles and then our orthotics department will give them molded insoles, which are replaced periodically because they will bottom out from the pressure points on the -- on the feet. And here are plastizote inserts which went into these New Balance running shoes. We like these because they come in four widths, so that we can accommodate these people.

Many times their foot size will change, that you'll start off with one foot size, and then because of the splaying of the bones and because of the fractures that take place in these neuropathic feet, the shoe size will change, so that you have to constantly assess the shoe size and also look for new pressure points in these areas.

We will sometimes use a Darco shoe. The problem here is that you have Velcro, and every time you use the Velcro or pull the Velcro closed, you might get a different type of compression. This is especially helpful for great toe lesions. Most great toe lesions are easy to heal because you can remove the pressure. It forces the folks not to spring off the toe. They have to walk with flat

feet here. But if you have metatarsal head or heel lesion, the Darco shoe will usually not be adequate. But for toe lesions or lateral or dorsal foot lesions, it'll usually be okay.

This is one that you might try with metatarsal head lesions. It relieves some of the pressure, although generally it's not going to be adequate.

This is another case to illustrate the necessity for debridement and also the issue about longevity of lesions. You know, how chronic is such a lesion, and are they more difficult to heal? This is a woman who came in last spring; she came in in April. She had had the lesion on your right since 1986, and the lesion on your left since 1989. And she was not debrided. She had been treated with whirlpool, antibiotics. But again, the *sine qua non* of therapy is primarily debridement and then pressure relief. Here are the shoes she was wearing. You can see she was scrunched into these shoes. There's absolutely no support at all; she's pounding away on these areas.

What did we do? Here I'm going to show you. This is the before, to show you the amount of callus and the callus on the -- on the

fourth metatarsal head. And here's the malodorous callus that was removed. She was not treated with an antibiotic, because clinically she was not infected.

And here she is following debridement. On the foot on your right, if you look at the dorsal aspect of the foot between the third and fourth toes, there's some granulation tissue. And this was a tract, actually, that was going right through the foot. So what we did here was, we just took a probe and pushed it through the tract, and then packed this through and through for about a week. And you can see this is what was done on a daily basis with the probe, and then just pulling saline gauze through with a hemostat.

And then she was put into a contact cast, and here she was after a couple of weeks of contact casting. And you can see good granulation tissue. There's no callus there, which indicates that the contact cast is relieving pressure and friction. And here she is healed. And this was from, I think, April 22nd until about June 15th or 16th. And these were ulcers that had been present ten years and seven years. But the two things that had not been done was -- were, there was no

debridement or no adequate debridement, and pressure was not relieved from these areas. She's now in shoes. It's been over a year. We see her at three-month intervals in Diabetic Foot Clinic, and she has not had a recurrence of her ulcerations.

Sometimes when you have heel lesions, you can go to one of the -- there are many orthotic devices. One that we will use is a Protho, which is a posterior relief ankle/foot arthosis. There's a problem with these sometimes, because again you're dealing with Velcro. You can see that at least before she's moving about, the heel is being relieved of pressure. And in this particular case, the wound did heal with this, with this device. So you have to be ingenious in the way you approach them to relieve pressure.

You know, as I said, in metatarsal head and heel lesions, our standard is contact casting, just because it's so difficult to relieve pressure. But in other -- we can do other things. We will do double Unabooting, we will put felt between Unaboot layers. So there are different approaches, but they all seek the same common ground, and that is to relieve pressure and friction after the lesions have been adequately debrided.

And in our hands, most of these ulcers will heal, between five and eight weeks.

The healing wound should be moist and quiescent, without exposure to toxins and frequent trauma. And this gets into the whole issue of topicals. We've gotten away from the hyperthins and the betadines and the peroxides, and we use strictly physiologic saline now, or an ointment base to maintain a moist wound environment.

Once the wound is clean, we do not use wet-to-dry dressings, because what you're going to do is interrupt the new epithelium. And I think that if you change the dressings b.i.d., once you have a clean dressing or a clean wound, you interrupt that wound healing. It's not necessary. Once you have a clean wound, you can change the dressing every day, every two days, maybe even three or four days. We will often just use saline dressings, and even with Saran Wrap over them to maintain the moist environment.

An issue about pulses, or a question about pulses. If pulses are present, even an abscessed foot can be saved. These neuropathic people don't have vascular insufficiency, and if they have pulses and they come in with an abscessed

foot, it's important that you really flay that foot and debride it vigorously to get rid of any pockets of purulent material. And you should be able to heal virtually all of them. These diabetics tolerate aggressive incision and draining. And it's really imperative that the abscesses be drained, rather than just have the patient treated with an anti- -- IV antibiotics. You've got to debride if you're going to heal these lesions.

How do you decide whether not an ulcer is infected? The question is, are there clinical signs of inflammation? Is there purulent or malodorous drainage? If the drainage is malodorous and deep, that's more likely to be an anaerobe. Most of these patients, if they get infected, are going to be infected with staphylococcus. But are there clinical signs of infection? In the diabetics the white count might not go up, they might not have a fever, but they will often complain of a flu-like syndrome, and they will also complain that the foot, which was previously insensate, has some sensation. They just don't feel right. But it's a clinical guess.

If we have somebody who comes in with a cellulitis or an abscess, that person is

hospitalized, debrided vigorously, and then receives IV antibiotics.

Bacteria are not equal to infection. If you culture these wounds, you're going to get four to five organisms from them. And you have to use, again, your clinical acumen to determine is this a true infection or is it just colonization?

The last issue that I just wanted to mention briefly is diabetic osteopathy on X-ray and its confusion with osteomyelitis. I think that many folks are diagnosed with osteomyelitis who, in fact, don't have true osteomyelitis, or if they have some peripheral bone or even bone infection, that can revert as the wounds heal. And we've seen many people who have had a diagnosis of osteomyelitis, they're not treated with prolonged courses of antibiotics, the wounds heal, and when you re-X-ray them, some of the -- some of that bone has been reconstituted. Some of it will remain with defects, but the patients do not have any clinical evidence of osteomyelitis. And in the past what we had seen was patients who had failed to heal, and it was felt that they failed to heal because of osteomyelitis, when in fact they had not been debrided adequately, pressure and friction were not relieved from the

lesions.

How do you make the diagnosis of osteo? If you probed a bone, you're more likely to have osteo. And what we do, if we can probe the bone and we have a soft bone in the foot that we can see, that soft bone will crumble with rongeuring or even curettage, we will just remove the soft bone down to hard, bleeding bone, and not prolong it with IV antibiotics or even long courses of antibiotics. And we've seen innumerable patients heal with this method. So if we have exposed bone, we will just remove the bone, just rongeur it out to good, bleeding bone.

So again, if you're aware of the clinical and diagnostic features of the ischemic and neuropathic ulcers, many limbs can be saved, and I've seen this repeatedly. It's important again to reiterate that you distinguish ischemic and neuropathic disease. If it's ischemic, they've got to go to the vascular people with the hope that they can be revascularized. If they're neuropathic, you must debride aggressively to get rid of all of callus and all the necrotic material. And then in your therapy it's basic wound care, consisting of a moist environment, usually with saline, and pressure

and friction relief, which can be a real art.

Thank you.

MR. McGUIRE: We can have -- we can have the lights, please. We're pretty much on time. If there are two or three questions from the Advisory Committee, I think they can be dealt with by any of the previous speakers.

Yes?

MR. LIPSKY: I'd like to address Dr. Miller. It's an outstanding presentation, and you've confirmed so many of my biases that you must be right.

The one area that I would like to question you on with my background being in infectious diseases, the only thing you said that I have any dispute with is the need for hospitalization and intravenous antibiotics. If a patient needs to be off of his foot, there are cheaper places to get him off his feet than the hospital, if that's the only reason.

Secondly, IV antibiotics. What we care about is the serum level of the antibiotic. And we have new oral agents which get very high serum levels, extremely high bioavailability. And therefore, intravenous therapy may be unnecessary.

We treat lots of these patients at home with oral agents, even with relatively serious infections.

MR. F. MILLER: Right. Thank you. And I would, you know, confirm what you've just said. That's precisely what we do. When I -- when I made my statement, I was talking about the abscessed foot -- you know, the foot that comes in that's red and hot, and you open it up and you get purulent drainage. But we work closely with Infectious Disease, and we do treat patients on an outpatient basis for the most part. Thank you.

MR. McGUIRE: Dr. Harkless.

MR. HARKLESS: On assessment, in your assessment, one thing I think you left out is why did the ulcer actually occur? And I think that's something that's oftentimes overlooked. Because I think the limited joint mobility and the flexibility and rigidity of the foot plays more of a significant role in idiopathic genesis than anything else. Yes, I can heal the ulcer, but what caused it? I see that as a most common reason for recurrence. And lack of evaluation can lead to that recurrence.

MR. F. MILLER: Yeah. The point was, what about the flexibility of the foot? These people do have collagen defects. You know, they

talk about the cross-linked things that --

MR. HARKLESS: Well, you showed some analysis of the hallux and phalangeal joint. I would surmise that the most common idiopathic genesis is usually deformity, generally hallux valgus, hallux-interphalangeal subductus, hallux extensis, and probably interphalangeal sesamoid. I very seldom will see an ulcer without one of those particular deformities. And without recognition of it, it will recur. It's not necessarily the skin; it is pressure. But something caused the pressure, usually deformity.

MR. McGUIRE: Yes? Dr. Bergfeld had a question.

MS. BERGFELD: Yes, Fred. I wanted to ask you a question about the statement you made regarding the wound and the infection and making a difference between infection and colonization. I wonder if you can define "infection," define "colonization," and perhaps define what the presence of the bacteria is actually doing. Are the numbers important? The type of bacteria? Is there really a difference if you have active bacteria in the wound?

MR. F. MILLER: Yeah. First of all, we haven't looked at numbers. Well, you know, what

about the numbers of bacteria and the types of bacteria?

When the patients come in, in their evaluation, if they don't have signs of clinical infection, we don't even culture them. If we have a wound that doesn't seem to be healing properly, we will culture them and then, depending upon what we find, might use an antibiotic.

The one area where I think I've seen wound healing impeded, and we have a reasonable series now, is with pseudomonas. you know, they don't look clinically infected, but will grow pseudomonas. And then by using quarter-percent ascetic acid for a couple of weeks, we can frequently not have a pseudomonas-positive culture, and the wound will begin to heal. But other than that, unless they're not healing and we look at the -- look at the bacteria, that's not been an issue.

MR. McGUIRE: I have a question.

MR. F. MILLER: Yes?

MR. McGUIRE: Dr. McGuire.

I kept waiting for your mechanical devices slide. There are a number of -- there are a number of things that are being used fairly extensively for reducing the area of the wound. And

in some centers they seem to have -- they're very effective. Is that part of your practice?

MR. F. MILLER: Tell me, Joe, what types were you thinking about?

MR. McGUIRE: The hooks that you constantly keep --

MR. F. MILLER: Oh, I've not had any experience with them. You mean where you're bringing the wound edges together?

MR. McGUIRE: Yeah.

MR. F. MILLER: I've not had any personal experience with that.

MR. McGUIRE: There is a question here.

MR. LIPSKY: One other question. I agree with you entirely that debridement is absolutely crucial. And we've learned that sort of by the seat of our pants over time.

What I've observed is that neither I nor most of my colleagues were ever trained in medical school how to do that. It takes time to do that. I don't think most doctors know how or are willing to take the time. Who should do the debridement?

MR. F. MILLER: Right. The question

was, who should do the debridement? I guess it's the person in the institution with the most experience, you know, who's most facile at it. And you know, when you look at that list of folks involved with these lesions, you know, it's a whole host of people. And you go to one institution, and maybe it's the podiatrists who are taking care of it, another institution it's the surgeons. In our institution, it happens to be dermatology. And we work -- we have a joint clinic with orthopedics, but we work with all these other people.

And there's -- just as an aside, there's a joke in our -- in our institution that the orthopedic residents are sent to derm to learn how to debride, just because we're very, very aggressive. And that's what we've learned over the last decade, how important it is to debride aggressively, to use rongeurs, to use curettes, and to really clean wounds out.

And if we -- if we debride aggressively, we usually don't have to debride repeatedly, other than the calluses which form. And if they form, it's an indicator that we're not relieving pressure, we're not relieving friction.

MR. McGUIRE: The last question is

Dr. Tschen's.

MR. TSCHEN: I think we must not forget that we are seeing the end result of a multi-systemic -- multi-systemic disease. And if a patient is to have good diabetes control, the nutrition, weight control, and a bunch of other factors -- so I think we do not need to oversimplify by just doing the debridement and all the other things. We cannot forget about the diabetes control and all the other factors involved in there.

MR. McGUIRE: I'd like to thank the speakers and the Committee.

We will adjourn. We will have a -- we will not adjourn, we will have a few-minute break. The -- I don't know how that got out there.

The response of the sponsor will begin promptly at 10:00 o'clock.

(Recess at 9:42 until 10:05 a.m.)

MR. McGUIRE: Will people come in and have a seat?

(Pause.)

Good morning. If those of you in the back -- would those of you in the back of the room either sit down or leave or whatever?

(Pause.)

The sponsor's introductory remarks will be made by Jacqueline Coelln. Dr. Coelln.

SPONSOR'S PRESENTATION

INTRODUCTORY REMARKS

JACQUELINE A. COELLN, R.Ph.

MS. COELLN: Good morning. I'm Jacqueline Coelln, Director of Regulatory Affairs at the R.W. Johnson Pharmaceutical Research Institute.

On behalf of the companies involved with this program, I would like to thank the Committee and the FDA for allowing us to present the safety and efficacy data of Regranex gel. As you've heard already this morning, the Regranex gel is the first topical growth factor to reach this stage of development to treat chronic wounds.

The active material in Regranex is becaplermin. Becaplermin is the generic or USAN name for recombinant human platelet-derived growth factor BB. Characteristics of this recombinant protein are that it is expressed in yeast, and that it has an identical primary acid sequence to the native or endogenous PDGF-BB. It also has comparable biological -- I'm sorry -- comparable molecular weight.

As we heard from Dr. Mustoe, PDGF

plays a role in the wound healing process.

Excuse me while I change microphones.

PDGF plays a role -- is this on?

PDGF plays a role in the normal healing process. As such, it's important to note that becaplermin has comparable biological activity to endogenous PDGF. This has been shown through both mitogenic and chemotactic evaluation.

There are three dimeric forms of the PDGF molecule. It is the BB-homodimer that was selected for development, because it is the one form of the molecule that binds to all three receptor types.

Becaplermin is formulated into a preserved multi-dose gel formulation. As you heard earlier, the base of this formulation is sodium carboxymethylcellulose or CMC. This is an excipient, common to topical ophthalmic and eye injection products. Regranex gel is to be applied topically once daily as a thin, continuous layer.

Following my introduction, you will hear from Dr. David Steed. Dr. Steed is a professor of surgery at the University of Pittsburgh and a director of the Wound Healing/Limb Preservation Clinic. Dr. Steed is a past member of the Wound

Healing Society and has been on the board of directors of that society, as well as on the editorial board of the journal *Wounds*. We are very fortunate to have Dr. Steed as one of our principal investigators. Today Dr. Steed will be presenting some information about the diabetic ulcer disease, its complications, and the need for new therapies in this area.

Then Dr. Janice Smiell will present the results of our clinical efficacy and safety trials. Dr. Smiell is a surgeon who, after five years of work as the leader of a wound healing clinic, joined PRI as the associate director of Global Clinical R&D.

Dr. Basant Sharma will present following her. He is the senior director of Pharmaceutical Development at PRI, and he will provide some information on gel characteristics of this product.

And then I will discuss the labeling, proposed labeling for the product.

At the conclusion of all our presentations, we'll be happy to answer any questions that the Committee may have. To assist us, we have representatives from all the companies

and functional areas involved with this program, as well as some invited guests.

With us today are Dr. William Eaglstein, Dr. Martin Robson, both wound healing experts, and Dr. Allan Sampson, a leading authority on statistics.

Dr. Eaglstein is the chairman and Harvey Blank Professor of the Department of Dermatology at the University of Miami, School of Medicine. Dr. Eaglstein has done wide-ranging research in wound healing, and was one of the founding members of the Wound Healing Society.

Dr. Robson is a professor of surgery and a director of the Institute for Tissue Regeneration, Repair, and Rehabilitation at the University of South Florida, School of Medicine. Dr. Robson has extensive experience in clinical trials with cytokines, and is the past president of the Wound Healing Society. We are also fortunate to have Dr. Robson as one of our clinical investigators.

Dr. Allan Sampson is a professor and the chair of the Department of Statistics at the University of Pittsburgh. Dr. Sampson is a fellow in the American Statistical Association, and has

served on the editorial board of several statistical journals, including *JASA*.

In my introduction, I will review the key agreements between the sponsor and the FDA for this development program, as well as provide an overview of the companies involved with the program.

Throughout the development of this product, there have been numerous interactions with the Food and Drug Administration, and there are a couple of key agreements that I'd like to review for you.

In a series of meetings and conversations that initiated in May of 1993, it was agreed that the clinical package for the marketing application for Regranex gel would consist of a totality of data that includes one Phase 3 trial, one Phase 2 trial, and two supplemental trials. Also during this same time period it was agreed that the preclinical toxicology package was adequate to support the clinical program.

Also in 1993, the gel product itself was discussed, and it was agreed that the commercial product would be a low bioburden formulation. And what that means is that it's a gel product that is virtually free of microorganisms, and Dr. Sharma

will speak about this later.

We also discussed with the Agency the design of the commercial facilities, which are of course now built, and they were found to be satisfactory.

There are several companies involved with this program.

The drug substance was developed by and is produced by Chiron Corporation.

The gel formulation and the clinical trials are the responsibility of the R.W. Johnson Pharmaceutical Research Institute.

This product is manufactured by OMJ Pharmaceuticals, who will be the license holder.

And upon approval, this product will be distributed by McNeil Pharmaceutical.

These three companies involved with the drug product are all Johnson & Johnson affiliates.

We believe, from the data that you will see today, that Regranex gel is safe, efficacious, and will provide a new therapy option to patients and physicians to treat this potentially debilitating illness.

I'd now like to introduce Dr. David

Steed, who will discuss this disease.

DISEASE OVERVIEW

DAVID L. STEED, M.D.

MR. STEED: Thank you, Jacqueline.

My name is David Steed, and I'm a surgeon at the University of Pittsburgh, and I'm the director of the Wound Healing/Limb Preservation Clinic. I am honored to be here today, and I appreciate being invited.

In 1987, when Richard Simmons became the new chairman of the Department of Surgery, he suggested that we start a clinic, and suggested that we call it the Wound Healing/Limb Preservation Clinic, recognizing that although there were many patients with diabetic ulcers for whom we cared, there was no central clinic where new techniques could be tried, where patients could be cared for. And he suggested that we call it the Wound Healing/Limb Preservation Clinic, since the reason we try to heal these ulcers is to preserve their limbs.

Now, if you look at all the patients that we've seen over the past ten years, this is the breakdown.

You heard from Dr. Mustoe earlier that there were three common diseases of the lower

extremities. At our clinic, which has over 7,000 clinic visits per year, 27 percent of those patients had diabetic neurotropic ulcers, 41 percent of those patients had venous stasis ulcers, 13 percent have ischemic ulcers, and the remainder have a variety of miscellaneous disorders leading to ulceration, most commonly dermatologic problems.

Well, as I said, we average over 7,000 clinic visits per year at the University of Pittsburgh, and 27 percent of the patients have diabetic ulcers. We offer a variety of therapies, and all the therapies that Fred Miller spoke about earlier, but we still have patients whose wounds just won't heal.

Now, to put this problem into perspective -- and these numbers are from the American Diabetes Association last year -- there are 16 million patients in the United States with diabetes. Fifteen percent of those patients will develop an ulcer at some point during the course of their disease. If you take 15 percent of 16 million, there are 2 to 3 million patients who are at risk for ulceration. At least in western Pennsylvania, it's the most common reason for hospitalization in the diabetic population -- that

is, complications of a diabetic foot ulcer. It is no longer control of glucose, as we manage glucose better as an outpatient.

It's the leading cause of leg amputation in this group -- the leading cause. Despite all our therapies, diabetic ulcer is still the leading cause of amputation.

And the most staggering statistic is the last line: if you have a diabetic foot ulcer and you lose your leg, half of those patients will lose the other leg within three to five years. Now, you might think that the patients that lost their leg are patients -- are a group of patients whose physician and patient have -- the physician and the patient themselves have a heightened awareness of this problem. And despite that, half of them still lose their other leg within five years.

Well, the problems come from neuropathy and vascular insufficiency, as Fred Miller told you, and I will restrict my comments to those patients who have neuropathy as the cause of their ulceration. In our clinic, that amounts to about 70 percent of the patients. Twenty-seven percent of the patients have neuropathy and ischemia, and perhaps 15 to 20 percent of the

patients have ischemia alone as the etiology.

Now, this is an ulcer, and you saw some ulcers from Fred Miller. But they're commonly on a plantar surface. Here, this is an ulcer at the base. You can see that this toe is markedly deformed, as Dr. Harkless pointed out earlier. There's limited joint mobility.

Now, treating these ulcers is not simple, and if they're not treated properly, not only do they not get better, but the problem worsens.

This is a patient who had an ulcer beneath the third metatarsal head. And one of the orthopedists in our town reasoned that if you take out the metatarsal head, there can no longer be a pressure point. So they took out the third metatarsal head, they did not put them into protective footwear, as you saw, and what happens is, this patient develops what's called a transfer lesion. The weight-bearing was now on the first and fifth metatarsal heads, so they traded one ulcer for two. So if they're not treated properly, not only do they not get better, they worsen.

And the neuropathy is both motor and sensory neuropathy, as you heard from Dr. Harkless.

They have limited joint mobility. the small muscles of the foot don't hold the bones into proper alignment, the foot develops an abnormal shape. Because they don't have sensation, they have unrecognized pressure points. The have irritation of the skin, and if it lasts long enough, they will come to ulceration.

Now, most are on the plantar surface. They may extend down to the tendon, the joint space, or the bone. I believe that deeper ulcers are more difficult to heal; these are the ones that commonly involve the tendon, joint space, or bone.

And I'd just like to talk a moment about staging. And if during the course of the day, if we have a discussion of staging of the diabetic ulcers, I would like to point out that at the University of Pittsburgh when we keep patient records, we don't use staging. And the reason we don't is because some people say a Stage II, and you think you know what a Stage II is, and the other person believes they know what a Stage II is, but in fact they're looking at different staging systems or they don't know the staging system well.

So we use descriptive terms. We give the depth of the ulcer, the size of the ulcer, and

we say which tissues are involved. Does it involve the joint? Does it involve the bone? So that if you went back to our records and tried to apply a staging system, you could do it in every patient, because we keep careful records of what's involved. But we don't use the staging, because if other physicians read the records and they don't know the staging system, they may not understand what tissues were involved.

Now, how do we treat these ulcers? First and foremost, we treat the diabetes. And I believe that if your diabetes is out of control, there's a higher incidence of limb loss, and that's been shown.

We make an accurate assessment of blood supplies. You heard from Fred Miller. We search for and treat infection. We make sure they're absolutely non-weight-bearing. We make vigorous use of debridement, and we apply dressings.

Now, what dressings do you apply? We believe strongly in moist wound healing. There are a variety of creams and salves on the market, and one of our commonest dressings is saline-moistened gauze. But yet, there are a variety of creams and salves on the market, and they all are -- the reason

they stay on the market is because someone buys them, and the reason someone buys them is because a physician orders them. And even though you might talk about what are the standards of care or what is the standard care, there are a variety of creams and salves that are still being purchased because physicians order them.

So throughout the physician community there is no agreed-upon standard of care. Or let me say that even if there's an agreed-upon standard of care, perhaps by the American Diabetes Association, there are a number of primary care doctors who are still doing other things.

We put gauze over the wound. And we most commonly use saline-moistened gauze, but there are a variety of other gauzes and Vaseline-impregnated gauzes and other things that you can use.

And I'd like to talk for a moment about total-contact casting. Fred Miller brought that up this morning. And that's a specialized treatment, and I believe we need to put that treatment into perspective.

A total-contact cast is a molded cast with a very exact fit. It is not a simple cast like

you put on for a broken ankle. It has minimal padding; you pad the bony prominences, but you keep the padding to a minimum, so that it can be custom-fit to the patient's abnormally shaped foot. After you pad it, you apply plaster. Or at least we apply plaster, and we apply plaster so that the plaster molds to the foot. You allow the plaster to dry and then place fiberglass, and you place the fiberglass cast on it for strength.

The patient cannot walk on that foot until the fiberglass is dry, and we tell them to stay off of it for twenty-four hours. You have to remember that these feet are insensate, and if you mold this cast to the foot and the patient an hour later takes a step and changes the shape, they'll wear a new hole in their foot because the cast doesn't fit.

It requires a specially trained technician. I went to learn this technique a number of years ago; I went up to Penn State to see Jan Albrecht and Peter Cavanaugh at the Nittnany Valley Rehab Center, and I learned the technique from them. I sent two nurses and a patient care technician from our clinic to spend a day with them, and they came down to do it. And we have one person who does it,

and she's excellent. And so I'd like to point out that this is not something that you can do without special training, without understanding the technique.

And there are problems with it. If the cast doesn't fit properly -- remember, these are insensate feet -- it leads to abrasions and blisters.

If you put it on an unrecognized infection, even athlete's foot, you'll have infection out of control perhaps a week later when you take off that cast.

The patients have to be steady on their feet. If they fall, it leads to broken hips and other problems. Not only are some of the patients old, but some of the patients have arthritis, they have a motor or sensory neuropathy, so some of the patients are weak.

And a number of my patients, even the young ones, have diabetic retinopathy; they don't see well. So if they have a cast on their foot and they walk and trip over a crack in the pavement, once they're walking on their cast, if they trip over a crack in the pavement, they fall.

And so there are a limited number of

candidates. I'm not saying it's not a good technique; it's an excellent technique. But the number of candidates are limited.

It's very labor-intensive. I see 7,000 to 7,500 clinic visits a year for wound healing; 27 percent have diabetic neurotropic ulcers. In our clinic, every day I have clinic, I have about four patients who are having their cast changed from using total-contact casting. It takes special training to apply it. If you don't see enough patients to make it a technique, a cost-effective technique in your practice, you won't do it. At least in Pittsburgh, I have no primary care doctor or diabetologist who uses total-contact casting. They all take a shot to heal it themselves, and if they can't do it, send them to us.

I have patients who refuse total-contact casting because they can't shower. They say, "Doc, I'm in the business world; I meet clients every day. If I put a dressing on my foot, I can take a shower every day and have a clean wound that has no odor, and I can go out and work in the business world." But they can't do that if they can't jump in the shower. You can say, "You can

still shower with a plastic bag over your leg." That's true. But you can't get rid of the smell under the cast sometimes.

So the indications and the contraindications: they have to be free of infection, they must have an adequate blood supply, they must have a steady gait, they cannot have gangrene, they have to have minimal edema.

If they have an edematous foot and you put on a cast, and they elevate their leg and the edema goes down, the foot rattles inside the cast, and so they develop blisters and ulcerations from that.

It must be adequately debrided.

And they must be non-weight-bearing. We believe in this so emphatically that once we apply a total-contact cast, my cast technician, my patient care technician helps the patient from the examining table, which can be lowered and raised, into a wheelchair, and she takes the patient down to the car, which we have valet parking, takes him down to the car and helps the patient into the car, without seeing the cast touch the ground. And if she sees a patient put their foot down and believes that they bore any weight on it significantly, we

bring them back up and redo it, because we're so worried about rubbing a new ulcer.

So the ideal patient is generally younger, generally stronger, and motivated to comply with the program. They have the ability to walk with a steady gait. They're not infected. They have minimal drainage.

If they have too much drainage, the foot becomes macerated. It's difficult in Pittsburgh to put them on in August, in the "ninety/ninety" days, 90 degrees temperature and 90 percent humidity. I don't know what they do in Texas, but certainly the foot will become macerated. The patient must be willing not to shower and must be compliant.

I'm not saying it's a good technique; I'm saying it has limited application. And most primary care doctors don't do it. You need a specialized clinic where people have an interest.

Now, how many ulcers heal? Well, in general, taking all comers, 50 to 75 percent of patients with diabetic ulcers will heal in twelve weeks. But you might reverse that number: 25 to 50 percent don't heal within twelve weeks. So there's a large group of patients who don't heal and take a

longer period of time.

In the study where I was the lead investigator, that you'll hear about earlier -- later today, the F Study, we chose patients who had made no progress in healing for eight weeks. So we selected out ulcers that were more difficult to heal. We didn't want to try the product on someone that was going to get better anyhow.

And there's at least a 25 percent recurrence rate. And I believe that recurrence rate is related to patient compliance. If you get the ulcer heals and the patient's compliant with special footwear, and the patient behaves and inspects their feet and is careful about not getting athlete's foot or other things which lead to cracks between the toes, and they have their inserts checked, preferably every six months but certainly every year, and they wear comfortable shoes that are soft, then in fact the recurrence rate is low. And if they've got an ulcer from their golf shoes and if they heal the ulcer, and they go back to playing golf and put on their old shoes, golf shoes, they'll get another ulcer.

Well, there are multiple components to the care of the patient with diabetic ulcer. And

it's expensive: there's the cost of dressings, there's a variety of medications for you to choose, there are physician visits. Some of these patients, especially the ones that are infected, need to be seen once a week. There's transportation; if they have diabetic retinopathy, they can't drive, some family member or friend needs to bring them. If it's a family member, they take a half a day's vacation every time they come to the clinic. If they need to be admitted to the hospital, that's an expensive venture there. They need operations, they need debridements, they need amputation, they need bypasses, they need special healing sandals, they need custom shoes, they need special inserts, and they need a lot of family support. It's a complicated disease.

And there's still an unmet medical need. You heard about the techniques and the standards of care. Yes, that's true. But standard therapy is not always effective.

And what is standard therapy? If it's saline-moistened gauze and non-weight-bearing, why are there so many creams and salves still available on the market, and why are physicians ordering them? Perhaps we need to educate

physicians better on standards of care. And you're going to hear later that's a component of the program.

There are accepted preventive measures which the American Diabetes guidelines talks about and which physicians in this room will know. And we can't get doctors to use them.

I once gave a talk to a group of internists and asked how many asked every diabetic patient to take off their shoes and socks every visit. And the hands went up and we counted them, and it was 15 percent. So if you don't ask them to take off their shoes and socks, it's hard to know if they have an ulcer of the foot or if their foot is insensate.

And for all the things we talk about standard therapy, for all the things you hear, diabetic ulcer is still the leading cause of amputation in this group. There were 54,000 amputations in diabetic patients last year. Eighty-five percent of those patients had an ulcer at the time of amputation, 85 percent of 54,000. I got those numbers from the American Diabetes Association, and I believe they were in the letter you heard this morning.

It has a tremendous impact on the patient's life. They fear limb loss. And if you develop a diabetic ulcer, your worst fear will be that you'll lose your leg.

There's an incredible family burden in time: for dressing changes, to visit your parent or your sibling with an ulcer and to change their dressing every day. It affects your employment. It affects the patient's employment, the caretaker's employment. It's a tremendous economic burden, a financial burden for the patient, a financial burden for third-party payers, a financial burden for family members who have to take vacation or uncompensated time off work to help care for these members and bring them to the doctor.

And the impact of the amputation is even greater. There's operations, the cost of the operation and the impact of the operation, the morbidity and mortality of the operation, the long period of rehabilitation. They need an artificial limb. In Pittsburgh, at least, the first limb costs about $5,000, and 95 percent of the patients need at least one adjustment of that limb within the first year. And I get these numbers from our rehab specialist.

If they lose their leg and can't be independent, they need long-term care. Fifty percent lose their other limb. And if they don't need long-term care when they lose one limb, they need it when they lose the other. If they're still able to maintain their job after losing one leg, they oftentimes can't maintain their job after losing two. This is a very serious health problem. It has a significant impact on the health of the American population.

Well, we still have unhealed wounds with diabetic ulcers. It's still the leading cause of amputation, despite our best efforts. We still have a wide variety of treatments, despite whatever guidelines are issued. And there's still a need for better therapy.

Well, in summary, then, the diabetic ulcer is a complex disease. And the healing of the disease is complex, as you heard from Dr. Mustoe. It is under growth factor control; there's no doubt about that. Not all patients heal with standard therapy. And I believe, as a clinical investigator and someone who has participated in the PDGF project, I do believe that PDGF offers new hope.

And you have to put this into

perspective. This is a new treatment. The standard therapy controls the problems while the patient and mother nature heal the wound themselves. This is a new treatment to be added to what mother nature does for the wound. It's a new therapy.

You'll hear today that PDGF improves the healing by as much as 10 percent. Well, if you take the 15 percent of the patients with diabetes, or 60 million diabetic patients, and you add up 2.4 million wounds or 2.4 million patients at risk, if you can heal an additional 10 percent, that's 240,000 wounds. That's 240,000 patients that can be healed. And if 85 percent of patients with amputation, that have an amputation, are preceded by a wound, you're talking about healing patients and saving limbs that hadn't been healed before.

An important part of this program will be education. We need to educate the clinician on how to care for these ulcers, on the standard therapy, on what is needed. All those things that Fred Miller talked to you about are things that we do and things that many people in this audience do. But throughout the United States, a lot of places don't do them, people don't do them. They need the Geisingers and the University of Pittsburghs, but

they also need to be better educated as to what to do in their office.

Well, as a clinician and surgeon who cares for patients with diabetic foot ulcers, and unfortunately must perform amputations on these patients, I thank you for reviewing the information and data on this project. Thank you.

Our next speaker will be Dr. Jan Smiell. And Dr. Jan Smiell is a surgeon. She's the associate director for Global Clinical R&D, and she's going to speak about the clinical efficacy and safety results for this product.

Thank you.

CLINICAL EFFICACY AND SAFETY RESULTS

JANICE M. SMIELL, M.D.

MS. SMIELL: Thank you, Dr. Steed.

Good morning.

Since 1990, we've had over 1,300 patients in our clinical program. 915 of those patients have been treated with becaplermin gel. They have shown us, and we will show you that the becaplermin gel is efficacious in healing more diabetic ulcers than the placebo gel. And it heals ulcers faster than the placebo gel, and safely.

Our conclusions are based on our

Phase 3 pivotal trial and the combination of data from four twenty-week studies. These data also demonstrate a dose-related ordering of effect.

In these four studies we had 922 of our 1,006 diabetic ulcer patients. Our patient population was predominantly male and white, with a median age of fifty-nine years.

As Dr. Steed mentioned, 25 to 50 percent of patients do not heal their diabetic ulcers within twelve weeks. And it is these difficult to heal patients, difficult to heal ulcers in these patients, that we treated in our program.

They were all full-thickness ulcers, with a median duration of thirty weeks prior to our treatment. Most of them were on the forefoot, and the median ulcer size was approximately one and a half square centimeters.

My review will encompass the efficacy results of our four twenty-week studies, the Phase 2, Phase 3, and two supplemental studies, in chronological order, and the safety results in combined fashion.

In order to understand the progression of our program, let's take a few moments to look at the time line of these four trials.

Study F, our first trial, that began in 1990, was our Phase 2 trial, and it gave encouraging results about the efficacy of the becaplermin gel at the 30 microgram per gram concentration.

For the pivotal trial, the K or Phase 3 trial, we wanted to explore a dose response. Fortunately, before we started this study, there was -- there were results from documented pressure ulcer trials that showed a 100 microgram per gram dose was efficacious, and that a 300 microgram per gram does was no better. So when we designed that trial, we added the 100 microgram per gram concentration of becaplermin gel, expecting that we would see a dose response.

Also, the two supplemental studies that we designed included the 100 microgram per gram concentration of becaplermin gel. And those studies started while our pivotal trial was still ongoing.

All four of these trials are similar, with the exception of the treatment arms that were compared within each study and the baseline ulcer sizes that were allowed for entry. They were prospective, randomized, and blinded studies.

All patients were treated for a

period of time, up to healing or to twenty weeks, whichever occurred first. The study therapy was applied daily for twelve hours, followed by a second dressing of saline-moistened gauze. A standardized "good wound care" program was developed, and it was used with all patients, either alone as a comparator, or together with becaplermin gel or the placebo gel, which is really the vehicle gel.

This standardized care included an initial aggressive, sharp debridement of the ulcer, followed by debridement as necessary throughout the course of treatment, non-weight-bearing on the affected area, systemic treatment of any wound infections that occurred, maintenance of a moist wound environment, and assessment of a transcutaneous oxygen measure as a measure of limb perfusion. That's the TCPO2 that we heard about earlier.

All of these ulcers were chronic, meaning over eight weeks in duration, they were primarily neuropathic, and on the lower extremity. These ulcers were full-thickness, defined as extending through the epidermis and dermis and into the subcutaneous tissue. They were also free of clinical signs of infection upon entry.

Base line ulcer areas that were allowed in the studies varied from one to 100 centimeters squared in the Phase 2 trial, one to 40 centimeters squared in the Phase 3 trial, and one to 10 centimeters squared in a supplemental study.

We determined the adequacy of limb perfusion by measuring the transcutaneous oxygen tension or TCPO2, and that was required to be at least 30 millimeters of mercury.

In an effort to increase homogeneity, we carefully selected our inclusion and exclusion criteria. All ulcers that were of non-diabetic etiology or with underlying osteomyelitis or bone exposure, were excluded. We also excluded anyone with cancer at the ulcer site, an active malignancy, renal failure, systemic chemotherapeutic agent or corticosteroid use, and marked foot deformities.

The primary population that was analyzed in each of these four trials is the intent-to-treat population. And this is defined as the group of patients that were randomized, received at least one dose of study drug, and had any post-baseline data.

In all cases the primary end point was complete healing, which is defined as 100

percent wound closure, without any drainage or need of a dressing.

The secondary measure, time to healing, is the one that I'll be presenting today. First I'll go through the efficacy of our four trials, beginning with the Phase 2 study.

F, our Phase 2 study, was our first efficacy trial. It enrolled 118 patients. And as you can see, the 30 microgram per gram concentration becaplermin gel was significantly more effective in healing ulcers than the vehicle gel. Becaplermin gel healed 48 percent of the ulcers, compared to the vehicle, which healed 25 percent at a p-value of .016.

In all cases, our Y-axis here will be the percent of ulcers healed; the X-axis will contain the treatment groups as well as the number in each treatment arm.

Ten wound healing specialists served as the primary investigators in this trial. And it was this group that helped to design the standardized "good wound care" that was used throughout the program in all treatment arms, either alone or together with the study therapy. This study demonstrates that becaplermin gel is

efficacious.

In our pivotal trial, the K Study, we confirmed that becaplermin gel is efficacious. And as noted before, we define our preferred clinical concentration of becaplermin gel to be 100 microgram per gram, and now this is the concentration for which we are seeking approval.

The three treatment arms used to evaluate a dose response in this study were the vehicle, 30 microgram per gram becaplermin gel, and 100 microgram per gram becaplermin gel.

As you can see, the 30 microgram did not separate from the vehicle in this study. The becaplermin gel, 100 microgram per gram, performed statistically superior to the vehicle gel, with a p-value of .007 in a one-sided .025 level test. This is clearly significant.

When we look at the life table plot for the time to healing, we see that the 100 microgram per gram concentration becaplermin gel, the solid green line, begins to separate from the vehicle at about eleven weeks. Becaplermin at 100 microgram per gram significantly reduced the healing time, with a p-value of .013.

Since the vehicle did not achieve a

50 percent healing rate, we looked at the 35th percentile, its maximum response. Shown here are the results for the 35th percentile. And at the 35th percentile, becaplermin gel, 100 microgram per gram, healed ulcers about six weeks faster than the vehicle.

Once again, our pivotal trial shows that our preferred clinical concentration of becaplermin gel, 100 microgram per gram, heals 50 percent of chronic diabetic ulcers. This absolute difference of 15 percent over the vehicle means that becaplermin gel heals 43 percent more ulcers than the vehicle gel. And it decreased the time to healing by six weeks, or 32 percent.

We did two additional studies which differ from the previous efficacy trials: the DBFT-001, or vehicle effects study, which was designed to determine if the vehicle had a negative effect on healing, and DBFT-002, or resource utilization trial. In these trials, a standardized care alone was used as a comparator arm. This necessitated evaluator blinding between it and the active therapy.

We conducted the DBFT-001 study, the vehicle effects study, in response to a request from

the Agency. And in this 172-patient trial, we added a small becaplermin gel-treated arm to enhance our enrollment. This active arm did maintain a double blind with the vehicle gel in this study.

In our second supplemental study, DBFT-002, or resource utilization trial, we enrolled 250 patients and used as a comparator the standardized care alone. Therefore, it is not double-blinded, it is -- it is evaluator-blinded and has no vehicle control.

DBFT-001 did demonstrate that the vehicle does not have a negative effect on healing. In this trial, becaplermin gel healed a greater percentage of ulcers, and this does support our pivotal trial results.

In DBFT-002, there is minimal separation, but a positive trend for the becaplermin group.

We proved the efficacy of becaplermin gel in our pivotal Phase 3 K-trial, where the 100 microgram per gram concentration of becaplermin gel healed significantly more ulcers than the vehicle, and healed ulcers faster than the vehicle gel.

There were differences in responses across these four trials, not only for the

becaplermin gel groups, but also the comparator groups. This can be expected in this complex disease state, with so many factors that can influence healing.

So to explore this and to better understand our data, we looked at both the combination of data across our trials and the factors that affected healing in our trials. Let's look first at the combined data, and then I'll present the factors that may have affected healing in our trials.

To more precisely assess a dose, or really, concentration response in these four trials which are of similar design, we combined the data using two methods: a straightforward pooling of the entire intent-to-treat population, and logistic regression of the ulcers and the size range that was in common across all trials -- that is, the one to 10 centimeter squared size range.

This straightforward pooling illustrates clearly the dose-related ordering of effect from vehicle to the 30 to the 100 microgram per gram concentration of becaplermin gel. It is also clear that the 100 microgram per gram becaplermin gel is superior to all the control

treatments.

We also see a concentration or dose-related response in the time to healing for the pooled intent-to-treat population. Again, the 100 microgram per gram concentration had the fastest healing time. So the straightforward pooling results for both efficacy measures, complete healing and time to healing, suggests this dose-related ordering of effect, with becaplermin gel having the greatest efficacy.

A statistical analysis here is complicated by the sparsity of data that we have in the largest ulcer sizes, and this does make it difficult in a formal analysis to generalize these results across that entire population. But if we look at the regions where we had the most significant amount of data -- that is, the size range that was in common across all trials, the one to 10 square centimeters, then it is statistically justifiable. And this actually represents 95 percent of our patient population, or 876 patients. And I'm sure that, as most of our panel members have heard or seen here today, the typical diabetic ulcer really is under 10 square centimeters.

A formal combined analysis was

performed using logistic regression modeling. The goal here was to more precisely assess the relative efficacy of the 100 microgram per gram concentration becaplermin gel across all four trials.

We also wanted to confirm the dose-related ordering of effect that was seen in the straightforward pooling. This model shows that becaplermin gel, 100 microgram per gram, again in the solid green line, is statistically superior to the vehicle, the dotted yellow line, across the entire range from one to 10 square centimeters, with a p-value of .007. Also note that there is a consistent dose-related ordering of effect here across the entire range. And note that with decreasing size, there is increasing efficacy.

Again, this axis is the estimated incidence of complete healing, and these are the baseline ulcers' size in intervals up to 10 centimeters square.

If we examine the response for our median baseline ulcer size of 1.5 square centimeters, we see that the estimated incidence of healing for the 100 microgram per gram concentration was 50 percent, and for the vehicle, 36 percent. This is consistent with what we observed in our

pivotal trial result of 50 versus 35.

Kaplan-Meier estimates for the time to healing, again at the 35th percentile, are also consistent with the pivotal trial results, where becaplermin gel heals ulcers about six weeks faster than the vehicle.

So we demonstrated efficacy in both our pivotal trial, the K Study, and the combined data, and we saw the dose response relationship in the combined data. No matter which data we look at, that from the pivotal trial or the combined analyses, we see that becaplermin, 100 microgram per gram, performed better than the controls in all cases.

Again, since diabetes is such a complex disease state and healing may be influenced by so many factors, as we've seen over and over here this morning, we conducted exploratory analysis utilizing those factors to try to -- in an attempt to better understand our data.

We looked at all of these factors, some that were mentioned today, plus a few more. We tested them for significance across our studies, as well as across all treatment arms. We found that out of all of these factors, four of them

differentially affected healing in our trials. The most important was baseline ulcer area; the other three: infection control, transcutaneous oxygen tension or TCPO2, and protocol compliance.

Because there is a question before you today regarding the amount of drug to be applied, before I discuss these four factors I'd like to share with you our drug usage data. Our drug usage data will demonstrate that the efficacy of becaplermin gel is not influenced by the amount of drug applied, and it also illustrates that measuring the gel should not be required.

The directions for use indicate that a sufficient amount should be used to cover the ulcer area with a thin layer of gel. This slide shows both the means the range of the gel applied, as a percent compliance in each of our four twenty-week trials. These are the four twenty-week trials' active drug arms, and these are the percent compliance along the X-axis. Note that percent compliance was calculated by taking the actual use, based on the tube weights at dispensing and retrieval, over what would be the prescribed use, times 100.

In our first three trials, the F, K,

and 001, a formula was used to calculate the amount that was to be applied to the ulcer, and this formula used as a basis the length times width ulcer area at each visit.

In our fourth study, DBFT-002, descriptive instructions were given -- that is, they were instructed to apply a layer that would cover the ulcer at the thickness of a dime. Whether calculated or not, the amounts that were used varied widely.

The mean of the percent healed on this graph is demonstrated by the green square, and the mean for the non-healed by the red squares. What you can see on this graph is that there is no suggestion that healing is correlated with the amount of gel that was applied.

On this slide, the relationship between the amount of gel applied and the outcome is shown in more detail. This shows, again, percentage of drug compliance does affect efficacy of this product.

We saw a similar result when we looked at this another way, using the amount of becaplermin per centimeter squared of ulcer area per day. Therefore, as with any other topical product,

the concentration, and not necessarily the quantity, is associated with efficacy. Measuring should not be required, since the amount applied in our studies does not affect its efficacy.

Let's get back to the four factors which differentially affected healing in our studies. Protocol compliance and transcutaneous oxygen tension had an impact on our DBFT-002 study, which had the highest incidence of protocol non-compliance, and the most physiologically unlikely TCPO2 values measured.

The separation between the 100 microgram per gram concentration becaplermin gel and the standard care is larger when either the population that is protocol-compliant or has valid transcutaneous oxygen tension measures are examined.

Infection control was found to be important when we looked at our F Study, the Phase 2 study. In that study, the 30 microgram per gram concentration of becaplermin gel had much better infection control than the 30 microgram concentration in the pivotal trial, the K Study. And this may help explain why the separation that was seen in our Phase 2 trial was not repeated in the pivotal trial.

The most important factor of all is baseline ulcer area. To evaluate this, we plotted our results for the percentage healed, centimeter by centimeter, to see where the most consistent responses occurred. And what did we see? On this bar graph we have percentage of ulcers healed on the Y-axis, baseline ulcer areas' intervals from zero to 10 and greater than 10. The n-values for each of these groups are represented by the numbers below.

We identified that the group with ulcer areas up to and including 5 square centimeters had the most consistent response during this twenty-week treatment period. The incidence of complete healing in each of these intervals is greater for the becaplermin group than it is for the vehicle. This zero to 5 centimeter squared included 84 percent of our diabetic ulcer patients, or 774 patients.

It's also important to note that the values, or the less consistent response seen here in the larger ulcer sizes, are probably related to the sparsity of data in these ranges.

If we look back at the individual studies for the less than or equal to 5 square centimeter baseline ulcer area, we see that the

results for all four trials are more consistent for the treatment groups within them, and there is a larger separation between the comparators and becaplermin gel, especially in this DBFT-002 study.

Our proposed labeling does address this, the diabetic ulcers with the most consistent response -- that is, the ulcers with baseline areas up to and including 5 square centimeters by planimetry.

Efficacy was demonstrated in our pivotal trial, as well as in the combination of the data. We proved the efficacy of the 100 microgram per gram concentration of becaplermin gel by showing increased incidence of healing and decreased time to healing. We noted a dose response relationship in the combined data. And with the analysis of the factors that affect healing, we've confirmed the importance of good wound care, and that the most consistent response can be seen in ulcers with baseline areas up to and including 5 square centimeters. We know that becaplermin gel works.

Now let's look at its safety. I'll review the safety profile by summarizing our Phase 1 trials, ulcer recurrence, and adverse events. For the sake of completeness, I'll also include the

adverse events experienced in our pressure ulcer trials.

We have three Phase 1 trials: A, B, and C. Forty-five healthy volunteers applied becaplermin gel, saline, or vehicle gel to their intact skin in Study A, abraded skin in Study B. And Study C was a challenge study: volunteers applied the study drug to their skin for a period of two weeks, then after a one-week drug-free period they were rechallenged at a separate site. They were then examined for signs of sensitization.

We performed two other studies to demonstrate the absorption of becaplermin. These are PHI-005 and PHI-007. Both of these were two-week trials at the 100 microgram per gram concentration of becaplermin gel to full-thickness diabetic ulcers. PDGF levels were tested at three points: prior to dosing, after one dose, and after fourteen doses.

The results of these five trials show there is no irritation of intact or abraded skin.

There is no cutaneous sensitization.

There is negligible absorption -- and by "negligible" I mean that the post-treatment PDGF levels measured were within the endogenous PDGF

limits.

No neutralizing antibodies developed in these or any of the other clinical trials in our diabetic ulcer program.

Two patients did have non-neutralizing antibodies detected, and this may have reflected non-specific binding of the PDGF in the test.

Recurrence data was collected at three months after healing. This table displays the recurrence results available from our four twenty-week trials.

This bottom line shows you that there is no difference across the treatment arms. There appears to be no effect on the quality of closure when this growth factor is used to speed healing. It is felt, therefore, that it is, rather, patient non-compliance that contributes to recurrence.

Adverse events are listed in decreasing incidence with regard to the 100 microgram per gram concentration, the concentration for which we're seeking approval. This first list contains the data that we collected during all of our blinded diabetic ulcer trials. This includes the four twenty-week studies that we just reviewed,

as well as two shorter supportive studies.

Note that the incidences of these events are similar across all treatment arms. The nature of these events are expected in the diabetic ulcer population.

Likewise, the pressure ulcer studies show similar incidences across treatments, and events common to that population.

If we look specifically at the ulcer infection-related adverse events, we see that the wound infection-related events occur with equal or less frequency in the becaplermin-treated groups. Those groups are represented by the green and the blue bars in each of these types of events, compared to our comparators in the yellow and purple bars.

The same pattern is repeated in the pressure ulcer indication.

We also isolated the clinically relevant adverse events. These are neoplasms, since PDGF is a growth factor, and the application site reactions, since this is a topically applied product. None of the 1,006 diabetic ulcer patients in our program developed an ulcer-related neoplasm.

No one in the standard care group, and one percent in the vehicle and becaplermin

groups, experienced an application site reaction.

In summary, we have shown that with the topical use of becaplermin gel there is negligible absorption and no neutralizing antibody production in the diabetic population. Recurrence rates are comparable across treatments. Adverse events in general, and more specifically the ulcer infection-related adverse events and clinically relevant adverse events, are -- occur with similar frequency across the treatment arms. Becaplermin gel is safe and well tolerated.

In conclusion, becaplermin gel is safe and efficacious. We have demonstrated that becaplermin gel, with good wound care, heals 43 to 50 percent of chronic diabetic ulcers. It heals 10 to 15 percent more ulcers than the placebo gel, which represents a 30 to 43 percent increase over the vehicle gel.

And becaplermin gel heals ulcers about six weeks faster than the placebo gel, which represents a 30 percent improvement in the healing time.

I'd like to thank you for your attention, and now introduce Dr. Basant Sharma, who will discuss with you the product characteristics.

GEL PRODUCT CHARACTERISTICS

BASANT SHARMA, Ph.D.

MR. SHARMA: Thank you, Jan.

Good morning.

As per Agency request, I'd like to focus my presentation on three main points, starting with critical Regranex product characteristic. As you already heard, it's low bioburden, means virtually free from microorganism, preserved gel. I'll be sharing some data with you in respect to low bioburden and preservative characteristic. Like to finish my presentation sharing some information regarding clinical relevance of these formulations.

Before I start, I'd like to emphasize that this is the first topical recombinant growth hormone at this stage of development for treating the diabetic ulcer. This is a preserved multi-dose gel formulation. This formulation is also consistent with 1994 FDA tri-center publication guideline, applied once daily.

As you know, this is a multi-dose formulation. I'd just like to spend few minutes with you, try to give you the points considered during the earlier pharmaceutical development.

Multi-dose considerations focus on

two main areas. One is the tubes or container closures. The tubes are selected with small orifice, to minimize any potential environmental contamination. These tubes also have collapsible nature, so once drug is removed, they remain depressed, will not create suction. Once again, is minimized any potential contamination during use.

The second most important points in terms of formulation and multi-dose consideration is selection of the preservatives. The selection of preservative is important to maintain effective level of preservative activity. For Regranex gel the preservative agents are selected with the properties as bactericidal and fungicidal. Bactericidal and fungicidals are agents, kill both pathogenic and nonpathogenic bacteria and fungi, respectively.

Low bioburden nature and the preservative characteristics is monitored by two studies. The first one is microbial limit -- in simple word, it's bacterial contained. The second one is preservative effectiveness. Starting with microbial limit test, is the test for estimating number of viable aerobic microorganisms, as well as absence of designated microbial species. Those are

listed up here.

I'd just like to point that what the USP guideline is proposing and what are the Regranex specifications. USP guideline suggests less than 100 CFU or colony-forming units per gram. The Regranex specification is tighter, is less than 10 CFU per gram. Let me share the results generated so far on Regranex gel, data generated on routine basis.

So far we have experience of 36 lot manufactured, all made Regranex specification, which is less than 10 CFU per gram, as well as no microorganism record. This supported low bioburden nature of Regranex gel. In terms of preservative effectiveness, preservative are added for multi-dose, multi-use formulation to inhibit growth of microorganism. In simple word, this test is performed to demonstrate effectiveness of preservative, to ensure that preservative effectiveness remains throughout the shelf life of the product.

For Regranex, we confirmed the preservative effectiveness in three separate studies. The first one is USP or United State Pharmacopoeia guideline which involved single

microbial challenge. The second study is more robust, which utilized multiple microbial challenge. The third study is performed based on Agency request, which utilized mixed cocktail of organisms.

Starting with the first study, the test which is defined in USP required a microbial challenge of 105 - 106 CFU per gram, an organism which is specified in USP. In addition, we included also two additional microorganism, which is appropriate for this kind of formulation and intended use. As per USP, once this inoculum level have to be monitored at the interval of seven days, seven, fourteen, twenty-one, and twenty-one, twenty-eight days. Let me compare the requirement of the guideline as proposed in USP.

The test method is measured in terms of the log reduction required. For bacteria part of this test, USP required 2 log reduction at fourteen days. Regranex, once again, have tighter specification: we like to see at forty-eight hours a 3 log reduction, or 1,000-fold reduction of bacteria. For fungi, USP guideline require fourteen days, no increase. For Regranex, we like to see 2 log reduction.

So far, I described the test method

and the specification. Let's discuss the results.

When results is generated, is clearly support that no microorganism recovered at forty-eight hours. In terms of fungis, no organism recovered at seven days, as well as no organism recovered at twenty-eight days for both bacteria and fungi, which include yeast and molds.

The second study is multiple challenge. As I told you a few seconds back, is very robust study. It require the same number of microbial organism, which is 106, but in ten successive microbial challenge within fifteen days on the same gel product. Seven microorganisms used for this study, which is again same as listed before, represent aerobic and anaerobic microorganisms, and most commonly found in diabetic ulcers.

The outcome of this test is again consistent, as we saw with the USP in terms of bacteria: no organism recovered at even twenty-four hours, as well as no fungi recovered at seven days.

The last study, which required the mixed cocktail -- these are the four organisms used. We have partial result available as of today: no organism recovered at forty-eight hours. And test

is ongoing.

Now let me do the brief production history. So far, we have expense of manufacturing 36 lot, and all lot make microbial limit, Regranex specification. In summary, less than 10 CFU per gram, and no microorganism recovered, as well as the lots tested consistently, made Regranex preservative efficacy specification throughout shelf life. And these lots are tested at initial as well as eighteen-month interval, which is beyond the shelf life.

In summary, I would like to emphasize one more time the microbial specification, as well as the preservative efficacy specification, are tighter than proposed USP guideline.

In summary, I'd like to conclude, and with respect to pharmaceutical development, the selection of the right tube, which really minimized any potential microbiological contamination, as well as the right appropriate preservative system, ensure low bioburden product throughout shelf life.

Now, these are data generated in the laboratory. I'd just like to point out the similar situation, similar also finding observed in clinical studies: the patient treated with Regranex gel show

no difference in infection rate for those in standard care. Therefore, I'd like to conclude that multi-dose preserved formulation is well suited for treating diabetic ulcer.

Thank you very much for your attention, and I'd like to hand it over to Jacqueline Coelln.

LABELING AND CONCLUSIONS

MS. COELLN: Thanks, Basant.

In the final few minutes, I'd like to provide some information related to the proposed labeling of this product and then summarize our clinical data.

From the review of the factors that affect healing, there are three points that are noteworthy as it's related to the proposed labeling.

First, good wound care is important to ulcer healing.

Second, a consistent benefit has been demonstrated in the population which accounts for the majority of diabetic ulcers.

And third, the concentration of becaplermin gel, rather than the quantity, is associated with the efficacy of this product.

Our data show that good wound care

practices are an important factor with wound healing. This is a point that we have noted prominently in our proposed labeling, and specifically in our indications statement. In addition, as Dr. Steed alluded to earlier, the distributor company, McNeil Pharmaceutical, will fund or support education for physicians and other wound care practitioners in both debridement and good wound care practices.

In the presence of the inherent variability of this patient population, we have demonstrated efficacy. And specifically, we have identified a population with the most consistent benefit, and this population is indicated in our proposed labeling.

What you can see from the photo on the left is an irregularly shaped ulcer. For the purposes of our clinical trials, we used computerized planimetry to get a precise measurement of these ulcers. In clinical practice, what we'll most likely come across is a length-times-width measurement of these ulcers, which gives you the area of a square or rectangle. So this 5 centimeters square that you've been hearing us speak about today is equivalent to 7 centimeters squared

when it's measured by length times width. And this is what is reflected in our proposed indication statement, which I'll show you in a minute.

As Dr. Smiell presented from the drug usage data as well as the results of our clinical trials, it is the concentration rather than the quantity of gel applied associated with the efficacy. Therefore, as Dr. Smiell indicated, we believe measuring this gel with some sort of calculation is not necessary, and will add complexity for the patient. Rather, we propose that the gel be applied as a thin, continuous layer, sufficient to cover the area of the ulcer, using the qualitative measure, that thickness of a dime.

From the total label package, Regranex gel is proposed -- is indicated to promote the healing of full-thickness diabetic ulcers, which are defined as through the epidermis and dermis, and represent the patient population that we evaluated.

Regranex gel is safe and effective in increasing the incidence of complete healing and decreasing the time to complete healing. The most consistent benefit is seen in the diabetic ulcers up to approximately 7 centimeters squared, when measured by length times width, which is what I just

reviewed. And that correlation is also shown elsewhere in our proposed labeling. Regranex gel should be used in conjunction with good wound care practices.

Now let me bring you back to why we're here in the first place: there are 16 million people in the United States with diabetes. Approximately 15 percent, or 2.4 million people, will have a diabetic ulcer at some time in their life. About a third of these are chronic ulcers. And as we've heard presented today, this is a serious condition. Complications from these ulcers can be limb- and life-threatening.

We believe that Regranex gel will provide an active treatment to meet this medical need. Regranex has been shown to be safe for its intended use. The efficacy of Regranex gel, 100 microgram per gram, or 0.01 percent, has been shown to be efficacious in our pivotal K trial. The efficacy of Regranex gel, in specifically the 100 microgram per gram concentration, is supported by the analyses of the four studies combined.

In these studies, both pivotal K and the combined data, we have shown a 10 to 15 percent absolute improvement in the amount of ulcers that

heal. This correlates to approximately 30 to 43 percent more ulcers that will heal in these patients.

We'd like to thank the Committee and the FDA for your consideration of the benefits of Regranex gel, and at this time we'd be happy to answer any questions that you may have.

MR. McGUIRE: We have time for a few questions. The Agency is going to set up their projection apparatus, so there will be a little bit of chaos over in that corner of the room; just ignore that. And if any of you, any members of the Committee, have questions to direct to the sponsor -- yes, Bill? Dr. Rosenberg.

MR. ROSENBERG: I have a question for Dr. Smiell. Could we see your slide, I think 26 or 25 or 26 again?

MS. COELLN: Can you put up slide 26 from Jan's presentation?

MR. ROSENBERG: I think I didn't understand it clearly. I just wanted a little help. It shows, I think, the signs and baselines and percentage fields.

MS. SMIELL: Oh, it shows the --

MR. ROSENBERG: The square area of

ulcers, the baseline, as compared to the speed of healing. The three lines.

MS. SMIELL: The three lines? Okay.

MR. McGUIRE: Bill --

MS. SMIELL: Number 26.

MR. McGUIRE: Bill, you're not being recorded. You've got to talk into the microphone.

MR. ROSENBERG: I beg your pardon.

I'm just -- this is the one. As I understand it, the horizontal shows the ulcer size in square centimeters in the beginning. It looks to me --

MS. SMIELL: Yes.

MR. ROSENBERG: It looks to me like your best results were those that were zero ulcers at the beginning.

(Laughter.)

MS. SMIELL: Well, they don't touch that line. We did have ulcers within this range, because this was measurement by planimetry, whereas for entry they used length times width.

MR. ROSENBERG: I mean, an ulcer -- we're talking area, square centimeters of a tenth -- I mean, of a millimeter square area. I just -- was this -- I mean, are you happy with this slide? You

think this is valid data that was prepared the way the other slides should have been? I mean, you're willing to say that this is a good slide?

MS. SMIELL: Yes.

MR. ROSENBERG: Okay.

MS. PERRY: I do believe that --

MR. McGUIRE: Identify yourself, please.

MS. PERRY: The lines that are shown on this graph represents the results from our logistic regression model, so these lines represent the estimated healing rates throughout the whole range of ulcer sizes, from -- from slightly less than one square centimeter through the range of 10 square centimeters.

MR. ROSENBERG: I see. So these are not -- this is not a data slide based on measurements of ulcers.

MS. PERRY: These are not the actual measurements of the ulcers. These are the results from our logistic regression --

MR. ROSENBERG: I see.

MS. PERRY: -- model that show what the estimated healing rates would be.

MR. ROSENBERG: I see. So if there

was a tenth of a millimeter size ulcer, you predict it would have done very well.

MS. PERRY: Correct.

MR. HASHIMOTO: This is the problem. You say it's estimated incidence. That's not estimated incidence.

MS. PERRY: Those are the estimated percentage of patients that would expect to be healed.

MR. McGUIRE: Dr. Lavin.

MR. LAVIN: Yes; Phil Lavin.

Could you draw on there what the standard would look like as well, just with your -- with your hand, sort of show people what the standard would look like? Because that is a point that will come up this afternoon.

MS. SMIELL: The standard therapy had a shape that was not parallel to these, but had a steep downslope and then came to a near parallel beneath these three lines. There was some -- based on that transecting or crossing these lines, there were obvious interactions that occurred in this low range of ulcer size.

MR. LAVIN: Yeah. And just to finish off the point that I was trying to get at, the point

that that raises, is that in Study 2 you saw an absence of significance in terms of the incidence of complete healing. I believe it was 36 percent against 32 percent. And the point that I wanted to make there is that if you look at the population in Study 2, in terms of the size of the lesions, they were all principally -- I guess the average was around 1.3 to 1.5 square centimeters. So therefore, that would -- that difference would -- that absence in that level of size of lesion would not likely be significant in that Study 2, simply because of the results of this logistic regression.

MR. McGUIRE: A last question before we go to the Agency?

MR. WILSON: I don't think that -- this is Dr. Wilson. I don't think you presented it, but in the information that I received, the baseline data, about 79 to 90 percent were white. What was the remaining 10 percent in terms of racial composition?

MS. COELLN: They're going to pull those numbers out.

MR. WILSON: And are there any reasons to believe that racial factors may affect wound healing? I know -- I'm an ophthalmologist,

and specifically in glaucoma, and we believe that it does, in that field. And I'm just wondering if in this field whether there's any reasons to believe that racial factors, specifically maybe some of the co-morbid conditions, vascular conditions and so forth, that do seem to differ by race, could affect wound healing.

MS. COELLN: Dr. Robson would like to address that.

MR. ROBSON: I'm Dr. Robson from the University of South Florida.

We've actually looked at that over multiple clinical trials with cytokines, and have not been able to show that. Now, the underlying vascular problems that you're talking about, in most of these controlled clinical trials were eliminated, because we either used TCO2 or, in some studies, perfusion studies. And therefore, we may have eliminated that. But if we did regression curves based on race, on any of the clinical trials we've done, and when we added them all up, we were not able to show that difference.

MR. McGUIRE: Just the last question will be Mrs. Cohen, and then we'll go on to the -- to the Agency.

MS. COHEN: Thank you. Thank you for that question, because I wanted to ask it also, and I don't think we really got a full answer.

Who is responsible for good wound care? And have these patients been seen four or five months after the wound recovered?

MS. SMIELL: The primary investigators in these studies, as well as any sub-investigators that were seeing the patients, were responsible for delivering the good wound care, which was clearly defined prior to their beginning the study. The patients were seen at three months following healing, as the completion visit with those primary or sub-investigators.

MS. COHEN: When this cream hits the market, how certain are you going to be that the patient is going to continue with good wound care, if you're depending upon consumers?

MS. COELLN: One of the things that we believe goes in conjunction with the Regranex product is medical education. And we, as a company, are prepared to support medical education, to help train in this field.

MR. McGUIRE: I think -- thanks very much. I think we'll go on with the presentation

from the FDA.

Dr. Stromberg.

AGENCY'S PRESENTATION

SUBSTANCE BIOAVAILABILITY AND BIOBURDEN

KURT STROMBERG, M.D.

MR. STROMBERG: Good morning. My name is Kurt Stromberg. I am the BLA committee chairperson for this product.

I will review the drug substance, the bioavailability, and the low bioburden nature of this product. And to avoid redundancy, it will be brief, since much of this was covered by Dr. Sharma and Dr. Mustoe.

Now, if this looks complex and uninterpretable to you, it has served its point.

(Laughter.)

This is a slide from Jeff Davidson in which he attempts to, on the ordinate, describe a response, and over the abscissa, the length of days. And this is for an acute wound, and it progresses through stages: clot formation, resolution, inflammatory phase, granulation tissue phase to provide a foundation over which epithelialization can occur, a matrix development leading to remodeling. Growth factors are involved in this

process and are players in the orchestration of this growth factor cascade.

MR. THOMAS: Could you focus the slide a little?

MR. STROMBERG: I'm not sure you'd learn more if it was focused.

(Laughter.)

In any event, could we have the next slide, which I'll push myself.

Now, growth factors are involved in this process, and there are many that have been proposed; we have seven or eight here. Each has its own functional area of activity.

Platelet-derived growth factor's focus is on the fibroblast. PDGF mediates tissue repair through mitogenesis of mesenchymal cells -- namely, dermal fibroblasts, smooth muscle cells, capillary endothelial cells, chemo-attraction of these cells, including monocytes and neutrophils, and through the induction of extracellular matrix and the induction of metalloproteanases.

Now, we've all come to the wedding, but we haven't met the bride. PDGF is a basic cationic, hydrophobic dimer resulting from A-chain and B-chain formation, in which the dimer form is

required for biological activity. There are numerous cystine residues, leading to inter- and intrachain disulfide bonds. There are then three dimer forms: AA, AB, and BB. These chains are 50 percent homologous in amino acid sequence, reside on different chromosomes, and as ligands, interact with the tyrosine receptor, kinase PDGF receptors, either alpha- or beta-type, themselves residing on different chromosomes. The point to carry here is that the BB isomer is the most broadly reactive ligand for the PDGF receptor, interacting with alpha-alpha, alpha-beta, and beta-beta.

We've all heard of its low -- this product's low bioburden, preserved, multi-use nature. So I'll progress to why we feel that a low bioburden, preserved, multi-use product is acceptable.

First, the exception to the sterility requirement is permissible by legislation. And as we've heard before, it's in accord -- in accord with an FDA tri-center 1994 article. And we also know that the topical, chronic cutaneous ulcer indication means that it is a highly contaminated surface.

And at this point I want to correct an error that I became aware of with a discussion

with Dr. Robson this morning, in that the quantitative microbiology studies are done at a ten-fold dilution series, rather than the one to two or one to five dilution studies which I understood. And consequently, bacterial balance is even greater, in that it simply states that there is no growth at the 106 dilution. So this can go all the way up to a million organisms, and yet still it is considered, from the clinician's point of view, to be adequately debrided and ready for treatment.

Thirdly and specifically to the product, this aseptic manufacture is -- we have heard leads to a result in the microbial limits test which is below the level of detection in all Regranex logs to date. We've heard about the preservative system, and most importantly, that there is no observed difference in the clinical incidence of ulcer infection between the standardized care and the placebo or product arms.

As to bioavailability, we've also heard that in the clinical trials there has been no increase in the PDGF plasma levels after topical application of the product to patients with Stage III or IV diabetic ulcers; hence, Regranex treatment resulted in negligible systemic absorption.

I now want to list the actual people from the FDA's point of view who have done all this work for these two BLAs: on the Chiron side [*phonetics*]: Janice Brown, Becky Hackett, Gibbs Johnson; for Regranex: Debra Bower, Louis Marzella, Carolyn Renshaw, Jawahar Duare; and then those that have worked on both: Myrnal Chapico, Michael Fauntleroy, Mercedes Sarabian; our supervisors: David Finbloom, Karen Weiss, Bill Sweederman, and particularly we want to thank the Center for Drugs and Tracy Riley for setting this up.

I would now like to turn this over to Dr. Louis Marzella, who will review for the FDA the clinical and safety data.

CLINICAL AND SAFETY DATA

LOUIS MARZELLA, M.D., Ph.D.

MR. MARZELLA: Good morning, ladies and gentlemen, Mr. Chairman, distinguished members of the Committee.

The purpose of this presentation is to discuss the efficacy and safety of becaplermin. The main objectives are to review the key findings from the clinical trials and to discuss the Agency's interpretation of the findings. In addition, in this presentation we will review and set the stage

for the questions that the Agency is posing to the Committee. I will attempt to provide the rationale for the questions.

May I have the next slide?

It is helpful to once again review the -- provide an overview of the efficacy and safety studies. This slide indicates the -- in the first column, the shorthand notation for the studies, in the next column the number of subjects and roles are listed, and finally the treatment arms are listed.

The F Study was a Phase 2 study which compared the 30 microgram per gram formulation with the vehicle.

The K Study was the pivotal Stage 3 study in which the 30 microgram and 100 microgram formulations were compared to vehicle.

The 001 Study, as you've heard, was a Phase 2 vehicle effects study. The study was essentially designed to demonstrate that vehicle was an appropriate control and that vehicle was not harmful for wound healing. As you've also heard, this trial also included, for the purposes of enhancing enrollment, a small 100 microgram per gram formulation arm.

Finally, the last study is the 002 Study. And again as you've heard, this was a quality of life and pharmaco-economic study, a rather large study in which standard of care was compared to the 100 microgram per gram formulation.

The study subjects you've heard at length about. They're patients with diabetes mellitus. In the sponsor's presentation it was emphasized that the word "chronic ulcer" and "diabetic ulcer" was emphasized. I think it's appropriate to make the point that these ulcers were neuropathic. As you've heard from previous discussions, this excludes a number of patients that have vascular insufficiency.

The other point that I wish to emphasize is that the area of ulcers ranged between one square centimeters to less than 100 square centimeters. And the -- on this basis, the efficacy analyses that the sponsor discussed, which are based on -- not on the intent-to-treat population, but on subsets based on baseline ulcer area, are considered -- are to be considered exploratory.

Finally, the third point that I wish to emphasize in this slide is the staging of the ulcers. As we've heard, there are -- there's a lot

to be said for using descriptive terms for these ulcers.

If I may have the next slide --

I would like to emphasize that in this particular trial, patients with Stage III and Stage IV ulcers were enrolled. And the critical distinction -- and this will be the topic, by the way, of a question to the Committee. The critical distinction here is that the definition of "full thickness" for Stage III ulcers is not sufficient, because it doesn't take into account the critical component, that involvement of subcutaneous tissue is involved.

As Dr. Stromberg indicated -- and this is an important point, because as Dr. Stromberg indicated, PDGF is mytogenic for mesenchymal cells. And so based on the biology and the mechanism of action of this drug, and based on preclinical data as well as published clinical trials that appear in the literature, it is -- it is important to emphasize that this particular growth factor is not expected to be active in shallow ulcers. And it's also not expected to be active, perhaps, in ulcers that heal primarily by re-epithelialization.

If I may have the next slide --

The issue of dosing is another issue that I would like to highlight, because it forms the basis of a question to the panel. And the question particularly at hand is the question of measured dosing versus non-measured dosings.

In three out of the four clinical trials, the dosing was applied in a measured fashion by calculating the area of the ulcer and dividing by four. And in this manner, during -- at each of the visits the amount of becaplermin to be applied to the ulcer was recalculated. And it was the aim that -- the aim was to achieve a 2 or 7 microgram per square -- that should square centimeters for the 30 and 100 microgram formulations.

In only one of the trials, the 002 trial, the directions for usage were descriptive, and a thin layer of gel, a thickness of a dime, was applied.

Now, in the presentation, the sponsor drew the conclusion that the amount of drug was not correlated with outcome. I think that an additional interpretation of the data is actually that the question is still very much unresolved.

The very first slide that the sponsor indicated, which compared mean use, showed that for

the 100 microgram per gram formulation, with comparing the K Study to the 001 to the 002, there was a progressive increase in amount of drug used. And this correlated with a decrease in activity of the drug.

The next slide that the sponsor showed does make the point that -- on the basis of analysis of the 100 microgram per gram formulation, does make the point that the amount of drug applied did not differentially affect healing in the various -- in the various -- in the 100 microgram per gram formulation.

Additional data, which is presented in the submission in the BLA, can also be used to make the opposite point, particularly with the 002 Study, where an analysis of response based on the amount actually used does appear to correlate, at least numerically, with the outcome.

The basic point to be made, then, is that this issue is still unresolved, based on the data available.

The next slide.

Standard of care, you've also heard discussed at length, and this will be the topic of a question to the Committee.

Of particular interest is the issue of non-weight-bearing. As you've heard, in this particular study, appropriately, non-weight-bearing was customized to the particular patient. And the question that we will pose to the Committee, given the discussions we've heard of contact casting, is whether the Committee believes that the optimal standard of care to demonstrate the activity of becaplermin was used for all the types of plantar ulcers, irrespective of anatomic location.

Next slide, please.

As you've heard, again the efficacy outcomes where the primary outcome was the incidence of complete closure, clearly an objective outcome. The main secondary outcome was time to ulcer closure. And this was very predictive, and correlated generally well with the primary outcome measure.

The other main -- secondary outcome measure was relative ulcer area, defined as area at end point over area at baseline. This particular outcome measure did not correlate well with the primary end point, and it was not that predictive.

The issue -- the issue of ulcer recurrence, again is an issue that you've heard

discussed at length, and the reason for bringing it up is to highlight the fact that this brings the issue of durability of benefit. And there are two issues to be considered here.

One is whether the treatment, the experimental treatment, differentially affected ulcer recurrence. And it did not.

And the other issue is also that the ulcer recurrence bears on what we would like to define as durability of benefit. And in the sponsor's estimates of clinical benefit, the recurrent -- the ulcer recurrence was not factored in. And this accounts for some of the differences in the estimates of benefit that you will hear from the sponsor and the Agency.

For the efficacy analysis, again Dr. Smiell indicated an intent-to-treat -- intent-to-treat analysis was done. For the primary end point, a logistic regression was done; for secondary end point, a Cox proportional hazard analysis was done. And baseline ulcer size, center, and treatment were some of the other co-variants.

I think the point to emphasize here is that the analyses were all pre-specified, and the sponsor conducted the analyses as per protocol.

Next slide.

Drug treatment and compliance is an issue that I've already alluded to, and I bring this slide up to emphasize the definition of "percent drug compliance": medication weights are obtained at each visit, and the amount used, compared to the amount which was prescribed, was compared and multiplied by 100.

Now, with regards to the trial conduct and analysis, the bioresearch monitoring at CBER inspected selected study sites, and no problems were identified. So the conduct of trial is considered to have been good.

With regards to the efficacy and safety analysis, the other important point to make -- to make is that the -- and again, the analysis was performed as per protocol, and they were confirmed independently by CBER.

With regards to the discussion of the efficacy of results, the Agency will emphasize the results from the combined data, from a straightforward comparison of the incidence of closure in the combined data. I will also discuss the outcome of the 30 and 100 microgram per gram formulation across studies, and highlight the

variability of response, and compare that to the magnitude of the treatment effect. And this comparison, then, will bring some implications to bear regarding sample size.

As the sponsor indicated in their presentation, co-variant analyses are interesting to view -- to analyze co-factors which are responsible for healing -- for healing, of which we have heard there are many, were also important to compare to look for potential baseline imbalances.

And finally, again, the manner of application of drug will be discussed.

Next slide.

In the slides to follow, the -- at each column, the treatment arms will be indicated. They are -- they are standard: vehicle, 30 microgram per gram and 100 microgram formulation. The first column indicates the shorthand notation for the studies. And the -- in the rows, then, what is shown is the proportion of subjects that healed, and below, the percentage, the proportion by percent, is shown. And at the bottom, then we have again the summary of all the data, showing what the proportions were in all of the different arms.

The first contrast, treatment

contrast, that I'd like to highlight is the comparison between the 30 microgram per gram formulation and the vehicle. In the F Study, the 30 microgram per gram was shown to be efficacious. In the K Study, that, the statistical significance of the treatment effect, was not confirmed.

Next.

The next comparison that I would like to highlight is the comparison between the 100 microgram per gram formulation and the vehicle. In the K Study, this, this formulation, was shown to be efficacious. In the 001 Study, which as you've heard before, was not powered for efficacy. The results are consistent with activity for that becaplermin formulation.

The next slide highlights the contrast between the 100 microgram per gram formulation and standard of care. In the 001 Study, the 100 microgram per gram formulation was shown to be efficacious. In the 002 Study, the significance of the treatment effect could not be confirmed.

Next slide.

This slide highlights the ranges of treatment effect which were observed, the ranges of outcome which were observed in each study arm. And

the point to be made is that the range is relatively large. As one can see, for the vehicle, it ranges -- the outcome, the proportion of subjects with closure, ranged between 25 and 36 percent. There was a significant -- there was a range of between 36 and 50 in the 100 microgram per gram formulation.

The other point to emphasize is also the variable magnitude of the treatment effect. Again looking at the F Study, one can see roughly a 23 percent treatment effect. In the K Study, that treatment effect is approximately one percent.

Next slide.

And so on. So this slide, then, summarizes the issue of variability, and indicates that the variability was large, was present in each of the four study arms, it was fairly consistent in the range of about 10 to 13 percent, and the -- there was also a range in the size -- in the range of the becaplermin treatment effect. These are maximum, maximum effects, which were observed in absolute numbers.

Therefore, given the magnitude of the effect and the variability, then this speaks to the need for large sample sizes to demonstrate efficacy.

Now, the -- it's informative to look

at the factors and co-variants which affect wound healing. As has been discussed at length this morning very eloquently, a lot of these factors do affect healing. And these -- not surprisingly, all of these factors -- about sixteen of them were analyzed by the sponsors -- did correlate with outcome. And a number of these factors also were imbalanced at baseline, and adjusting for these imbalances in the -- in the analysis did affect the magnitude, the significance of the treatment effect, in any direction one chooses. So the point to be made, then, is that these analyses are *post hoc* analysis. And the best analysis to do is an intent-to-treat analysis.

Let me show you an example from the next slide, showing the effect of infection control on treat- -- the significance of the treatment effect.

This is for the F Study. And the slide makes two points: one is that there was an imbalance in infection control that favored the becaplermin arm, and the other point to be made is that the presence of infection control correlated with healing.

And at the bottom, then, the point to

be made is that if -- again, if this co-variant is co-factored in the analysis, that the significance of the treatment effect disappears.

Again, the point to be made is that, given relatively small trials, and given the number of factors that influence healing, that it's not surprising that, due to chance effects alone, that some imbalances may be present at baseline.

Next slide.

However, before I go to the next slide I would like show an overhead which also speaks to the -- to the consistency of the -- of the treatment effect. And what the -- the point that the overhead will make is that if one looks at the point estimate of the treatment effect, that the point estimate is always positive. So despite -- despite the fact that statistical -- statistical significance was not demonstrated in each trial, the point estimate was always positive.

And even if we cannot see this slide, I will just -- I will just make the point it's -- for the advisory panel, the slide is in your briefing package.

What it shows essentially the confidence intervals around the point estimates, and

makes the additional point -- it makes the additional point that the --

I'm really grateful for the effort, Dr. Mills.

Again, as I was indicating, what this shows is the point estimates of the treatment effect and the 95 percent confidence interval along those estimates. And the point again that I was making is that the treat- -- there's consistency of the treatment effect. It's always on the positive side. And for further evidence of consistency is the fact that even when the confidence intervals include zero and beyond, that the -- most of the range is on the positive side.

Thank you very much for the overhead.

We then come to the question, then, of, given what we know from these, from these clinical experiments regarding the magnitude of the effect and the variability, if one were to try to reproduce the efficacy data, a rather large study would be required. And this, then, raises the question of whether one large, adequately powered study is preferable to several studies, and to employing other approaches, such as trying to perhaps further use stricter entry criteria to try

to control the tremendous variability which we have heard exists in these kinds of trials, and which was demonstrated by co-variant analysis.

Next slide, please.

Now, I will now turn to the definition of the magnitude of the clinical benefit. And the magnitude of the benefit has implications, number one, for the sample size that is required to demonstrate efficacy in these types of studies, and also in defining what the clinical benefit is. And you have heard in the sponsor's presentation some numbers which will slightly differ from the studies that the Agency is presenting.

And the differences are basically based on the fact that the sponsor is including in their analysis the results of the pivotal study, as well as using *post hoc* analyses which are based on subpopulations, based on the -- based on baseline ulcer area.

In the analysis of benefit by the Agency, the emphasis will be on a straightforward comparison of the incidence of closure across all four studies. The concept of also "durable benefit" will also be used by the Agency to define "benefit." And I would like to emphasize that ulcer recurrence

is not part of the primary end point, but was -- there it was captured at three months after wound closure. But the Agency feels that it is appropriate to help define the benefit of the product.

In addition, the Agency is also emphasizing absolute numbers, whereas the sponsor also is mentioning relative numbers, which are also helpful to know about.

And finally, the Agency is comparison both comparison with vehicle, which perhaps is the best comparison from a clinical trial design, as well as the standard of care.

Now, the reason -- this slide shows the reason why a look and approach to define "efficacy" -- to define "magnitude of benefit" based on the combined data is perhaps necessary.

In the pivotal trial, the -- again, the efficacy of the 30 microgram formulation, the statistical significance of the treatment effect was not confirmed, but the efficacy of the 100 microgram per gram formulation was shown.

In the vehicle safety study, the Agency's concern regarding the appropriateness of the -- and safety of the vehicle were satisfied, but

the study was not designed to show efficacy of the 100 microgram per gram formulation.

Finally, in the pharmaco-economic study, which was an 002 study, which was a large study, the statistical significance of the 100 microgram per gram treatment effect was confirmed.

Next slide.

Therefore, the Agency, then, is looking at estimates, using combined analysis of four studies. In their presentation, the sponsor also used these values. And the use of the values are really method-dependent, and each method has really its strength and weakness. So the Agency is staying away from describing the statistical significance of these types of analysis.

This is, then, a straightforward comparison of the incidence of closure in all four efficacy studies. The incidence was about 43 percent in Regranex, and 33 percent in vehicle, so that the absolute difference between those two study arms is about 10 percent.

If one compares, then, the 100 microgram per gram formulation of Regranex to standard, one obtains a figure of about 15 percent in absolute numbers. And in relative numbers, this

is -- in the case, for instance, of Regranex versus vehicle, we're talking about 30 percent relative difference.

If one then factors in, as I indicated earlier, the issue of ulcer recurrence -- and the next slide will show that in more detail -- the incidence, we've heard, was about 30 percent in all arms, and indicating that treat- -- that healing was not effective in the becaplermin-treated arms. The durable clinical benefit that one obtains is an incidence of -- absolute incidence of about 7 to 10 percent -- 7 percent again compared to vehicle, and 10 percent compared to standard of care.

Another point that I would like to emphasize at this point is the issue of -- we've talked about theoretical concerns about the appropriateness of the ulcer stage in which becaplermin should be used. I would like to emphasize that there was no evidence of pathologic healing, such as -- such as, for instance, either ineffective or hypertrophic healing in these patients.

The next slide.

Then the final issue is the -- with regards to efficacy, is the issue of non-measure

dosing. And as I alluded earlier, the Agency regards this issue as being unsettled, and that the -- the phenomenology we have is that in the trial where non-measured dosage was used, the highest mean excessive usage of drug was applied, and the lowest efficacy was demonstrated, as compared to trials which used measured doses.

The other point to be made is that there was also considerable individual variability, both under- and overdosing, seen in all trials. And the -- one expectation might be that the variability would likely to be even more extreme outside of clinical trials, so that there might be the possibility of perhaps uncertainty about how to use the product.

In view of these uncertainties, the Agency is proposing that information on measured dosing be included in the label.

The next slide.

We would, then, find -- conclude regarding safety and tolerability of the drug, and our -- the Agency's analyses were essentially in agreement with those of the sponsors.

Of particular interest in these analyses was the incidence of infections because of,

in part, the formulation of the product, and in part because of the -- this was one of the most important concerns in a topically applied product. And if anything, obviously these studies were not powered to look at the incidence of these events. But if anything, there was a trend, as one would expect from ulcers. From an increase in incidence of ulcer and decrease in time to ulcer closure, there was, if anything, a trend towards decreased number of infections in the becaplermin-treated arms.

There are a number of deaths in these patients which were essentially related to the underlying disease state, and there was no imbalance that was apparent.

Some other theoretical concerns, as the sponsor indicated, were neoplasms, due to the fact that this is a growth factor and potentially could promote growth of neoplastic tissue. This was not -- this concern was not demonstrated in the clinical trials.

There was also theoretical concerns related to potential effects of this product on, for instance, arthromitous plaques. But the -- but as was discussed earlier, essentially this product is not bioavailable systemically. And indeed, the

safety data with regards to this theoretical concern was entirely benign.

Application site reactions were not -- were not of concern.

Again I'd like to emphasize the number of subjects which were studied, which was about 1,000 for the safety database.

With regard to the issue of antibodies to becaplermin, no neutralizing antibodies were demonstrated.

And the final slide, the conclusion, then.

There appears to evidence of treatment effect. The treatment effect is not statistically significant in all the studies that were performed by the sponsor. With regard to the observed magnitude of the treatment effect, in absolute numbers the durable benefit seems to be a 7 to 10 percent increase in the incidence of ulcer closure. And the safety profile appears to be benign.

Thank you.

DISCUSSION

MR. McGUIRE: Well, we've finished in very good order. I propose that we have about a

half hour of questions before we break for lunch. And if it's acceptable to everyone, we could ask both the Sponsor and the Agency questions.

Dr. Lipsky.

MR. LIPSKY: I want to ask a question about infection control. The term's been used numerous times. And neither this morning nor in any of the documents that I received has it been defined. I'd like to know --

I know that antibiotic therapy was allowed during the study for a variety of reasons, so that's probably part of it. But I'd like to know how it was defined, how it was measured. And since it appeared to potentially alter the outcome of at least one of the studies, I think it's critical to know.

MS. SMIELL: Infection control -- infection control was defined *post hoc* whenever the analysis was done, the exploratory analysis. And basically, anyone who had a wound infection-related adverse event during the course of their treatment was considered not to have control. And anyone who reached an average score of one, when we looked at six different factors in the assessment of the wound that were signs of infection, on a scale of zero to

three, was defined as not having adequate control. So infection control is like the opposite of a wound infection.

MR. McGUIRE: Yes, Dr. Wilson?

MR. WILSON: If I understood Dr. Harkless's previous comment, he felt that the etiologic basis for many, if not all, of these ulcers on the foot were due to some sort of deformity in the foot. And being that marked foot deformity was an exclusion criteria, I'm just curious as to how you defined foot deformity.

MS. SMIELL: We had a scale for foot deformities, where absence was one consideration, and then it was mild, moderate, and marked. And those were all defined in the protocol.

We did have 13 percent of our patients with midfoot ulcerations, and mild to moderate Charcot. So even -- you know, not all foot deformities were excluded.

MR. McGUIRE: Yes, Dr. Margolis?

MR. MARGOLIS: And as was nicely pointed out by Dr. Miller's slides earlier, post-debridement, these wounds are both deeper -- or actually should be deeper and should be larger than pre-debridement. Your 5 square centimeters and full

thickness, is that prior to debridement or post to debridement?

MS. SMIELL: That's the planimetric area post-debridement.

MR. McGUIRE: Yes, Dr. Drake?

MS. DRAKE: You know, I'm still a little -- I'm a little confused about the -- or unclear about the concentration. Clearly, in your K Study, the pivotal study, there was a statistically significant difference between the 30 microgram and the 100 microgram.

But if you look at just the F Study, and that was in the intent-to- treat slide you'd showed, showed 48 percent healing on the intent-to-treat versus in the F Study, which was at 30 micrograms versus just 50 percent at the 100 micrograms in your K Study. They were very similar.

And then further, if you look at the data that was presented by the FDA, where you had the incidence of 100 percent wound closure in four controlled studies, if you look at all four studies, in the 30 microgram it was 40 percent and in the 100 microgram it was 43 percent.

So I'm having a hard time over the whole balance of all the studies, understanding why

you think there's so much difference between the 30 and the 100 microgram dosing -- or concentration.

MS. SMIELL: Okay. The 30 microgram per gram concentration did have a significant difference in outcome in the F Study, as you stated. We did explain that the improved infection control, which was at an imbalance at that study compared with the K, the pivotal trial, may have helped add to that.

In addition, keep in mind that was the first trial, the Phase 2 trial, and that group of investigators were true subspecialists in wound care. Therefore, they had, as a group, an understanding of all the concepts of good wound care in that study, and had defined for themselves and defined the standardized care. So you would expect in a first trial, with that sort of intense group, that you would see excellent results, and if there was any efficacy at all to be seen with the drug.

In the 30 microgram group in the K Study, it still showed minimal positive effect over the vehicle. But that group, again, was of various subspecialties: medical, surgical, podiatry, they were all represented.

And Dr. Steed can give us some

insight about the -- he worked exclusively with the 30 microgram per gram concentration.

MR. STEED: Yes; Dick Steed. I was in large part responsible for the group of investigators in the 30 microgram study. I was the principal investigator, and asked to suggest other people who might be good investigators. Nine of the ten principal investigators were surgeons. They were people -- they were names that you will recognize from the literature as very experienced clinical investigators, had experience in clinical trials. These were really a blue-ribbon group.

We met and discussed debridement beforehand and debridement during the trial, and this was a group of people who really spoke the same language.

And I believe we took difficult-to-heal ulcers. And I believe that if you have an experienced group that can really -- that really understands wound healing -- we showed a benefit in the 30 microgram group. I believe that if you have a wider variety of physicians across all disciplines, that perhaps it takes the 100 microgram. But we really did show a difference. It was a blind trial; we didn't know.

But we sat in a room and argued about debridement for half a day. Those were a group of very specialized investigators, who I believe were able to bring out the effect even from 30 micrograms.

MS. DRAKE: Well, in follow-up to that, then, if you have -- if you're going to use 100 micrograms for the general approval process, assuming that not everybody's an expert who might use this drug, when you look at the total data, where I assume there was that -- the FDA presented the difference between the 30 micrograms and 100 micrograms was only three percentage points, and even that was only 33 percent over vehicle.

Now, my question is, as you -- as you expand your group of therapists, so to speak, you've shown a distinct decrease between the 30 micrograms and the 100 micrograms by moving away from experts. But you still had -- even in the 100 microgram group, I assume you had a certain degree of expertise in your clinical investigators. If you open this wide open, do you expect -- would you anticipate it to have even more dilution in efficacy?

MR. STEED: I only -- I can speak to

the 30 microgram trial, and perhaps not to the 100. But I can say that if you -- if you have a wider group of physicians, I believe that an important component of the program will be education of physicians. And the later trial involved other disciplines, other than just surgeons. And I believe that if you educate the physicians at large, as to what is standard wound care and how to use this product, I believe you can see the results achieved with the 100 microgram group.

And I'll let Jacqueline answer that further.

MR. McGUIRE: Dr. Mustoe.

MR. MUSTOE: Yes; I saw the -- you saw at the three-month follow-up in your studies you had a 30 percent recurrence rate, but that -- and you indicated that you had a six-week -- estimated six weeks speeding up the time of healing. The question is, what happened to the patients who had not healed at the three-month follow-up? In either the treated group or the untreated group, did they, any of those -- what percentage went on to heal? What percentage went on to amputation? And basically what was their outcome?

And then I have another follow-up

question.

MS. COELLN: I think Dr. Steed will address that question.

MR. STEED: I can speak for a clinic. It's distressing to have them not heal, because these are patients that hadn't healed in eight weeks. They came into this growth factor trial, and the ones that didn't go on to heal, some of them are still a problem. Some of them have gone on to amputation. But we really didn't have much more to offer. These were patients, at least in the F Study, where this group of investigators had really exhausted their treatments. These were patients that had not improved in eight weeks, so that when we offered them this, we had really tried the other things that we know to do.

I can't give you numbers, because I don't -- I haven't gone back and looked at them specifically. But I know the individual cases, at least at our site. Some of them have come to amputation. Some of them have died, specifically from myocardial infarction. I still have a couple with ulcers that are still present, and they've had a couple of facilitative infections that we've been able to control.

MS. SMIELL: I can add to that. We had an open label study to follow the Phase 2 and the Phase 3 trial, as well as the vehicle effect trial. And for people who didn't heal at the end of the twenty-week trials, they were allowed entry into the open label studies, whether they were a study ulcer or another ulcer that was full thickness. And at the end of those open label trials, which ranged in length from eight weeks to another twelve weeks, about 60 percent of all the ulcers treated with the 100 microgram per gram concentration of becaplermin gel healed.

MR. McGUIRE: Dr. Lipsky?

MR. LIPSKY: We've repeatedly heard about the importance of proper wound care, debriding the wound and removing the necrotic material prior to putting this substance on. I applaud the company's decision to move ahead with physician education. Nevertheless, we know that there will be instances where this product will be applied to wounds that have not been debrided or cleaned up. Are there any data supporting that this is a safe practice?

MS. COELLN: I think I'll ask Dr. Steed to present his debridement data from our Phase

2 trial. If you could put up Dr. Steed's backup --

MR. STEED: While she's getting the slide ready, I brought one additional slide with me.

After we had done the F Study, the 30 microgram study, as we were looking back at the data and discussing it when Dennis Donohoe was here, we talked about the fact -- and it was actually, I believe it was Dennis who was first to observe that the patients who were debrided, had more frequent debridements, seemed to heal better. Now, so we decided to go back and look at the records. This was done after the study was completed. It was not an end point, it was an observation.

And so we looked at the office records of every patients. So we looked at the office note for every patient, every visit, and saw, in nine of the ten principal investigators -- we looked to see was the wound debrided, yes or no?

Now, prior to this study we had agreed that before entry, we would have a vigorous debridement which would include necrotic tissue, all the callus. And in fact, we excised the granulation tissue which was there, theorizing that it was not good granulation tissue -- if it were good granulation tissue, the wound would have healed --

so let's get down to a good clean base and start again.

We also agreed that at each visit we would excise the callus. Now, you heard from Fred Miller that if you don't walk on it, you're less likely to get callus. But some patients still do get some callus. Because we didn't say at the investigators' meeting "Please note the amount of debridement," that wasn't noted. And usually the notes said, "Wound debrided," or didn't say, "Wound debrided." So we looked at every patient in the F Study, and was their wound debrided, yes or no?

Now, there were ten centers involved in that study. There were five centers that enrolled ten or more patients, and there were five centers that enrolled fewer than ten patients. And to review these data, I would like to pull the five centers that enrolled less than ten patients, and that will represent Center No. 3. The five centers that were less than ten in the data were pooled.

Now, this slide is very busy, but let me walk you through this, because it makes a very excellent point about PDGF.

Those six centers are listed here as -- the five that enrolled more than ten, and the

five that enrolled less than ten are pooled here. We looked at the follow-up office visits. Did the office notes say, "Wound debrided"? And so we looked at it for the recombinant human PDGF patients versus the placebo, which was the gel.

At Site 1, after the code was broken, 15 percent of the patients receiving PDGF had had an office debridement at their -- at 15 percent of the office visits and follow-up, there was a debridement. In the placebo group, there were 19 percent debrided, comparable groups.

So on down to Center 6, which had 81 percent of the office notes had a debridement, and the placebo group, 87 percent were debrided.

Now, looking for PDGF, the more office visits where there was a debridement, the more likely you were to heal. And there's almost a direct correlation, and I looked at this and said, "My God, it was the debridement, it wasn't the PDGF."

But you must look at the placebo group. As you notice, the numbers debrided per placebo were almost the same at every site -- very close. The healing rate improved with more vigorous debridement, but it was not as dramatic as it was

with PDGF.

But look at this: despite the fact that the percent debrided were the same, at every site the healing with PDGF was about double: twenty versus ten, fifty versus seventeen, sixty-four versus thirty-six, fifty versus seventeen, fifty-three versus thirty-two, and eighty-three versus twenty-five.

So what we learned was, number one, PDGF worked at every site at about double the healing rate. It about doubled it.

Also, PDGF must be applied in the context of good care. Now, I can't tell you the degree of debridement, and I can't tell you that that represents good care. What I can tell you is that debridement has some effect.

But notice that even if you were the site that debrided the least frequently, you would still double your healing rate for your site if you used PDGF, twenty versus ten. Now, you might argue that you'd rather come to Site 6 and get placebo than receive PDGF at Site 1. But --

(Laughter.)

And that might be true. But what I would say to you is, no matter what site you

visited, if you were to be enrolled in that study, you would have always fared better drawing PDGF as opposed to drawing the vehicle gel, because it doubled the healing rate.

So these data were collected retrospectively, and I admit that. We don't have data on the degree of debridement, and I admit that. But we did agree prior to the study on how to debride these wounds initially and at the office visit. Nine of the ten PIs were surgeons, they were very good surgeons; you'd be happy to them for your doctor.

And looking back on this, this is the closest thing we have to objective data on debridement, to say that it's of benefit.

The question comes up, what about a wound that doesn't get any debridement? And that will happen. But I would hope, as -- this is a time of increased awareness of diabetic ulcers. I would hope that primary care doctors, or others who don't feel comfortable debriding a wound, would look at a wound, and if there's necrotic tissue or if there's callus, they need to involve their surgical or dermatologic or podiatric colleagues to debride this wound for them. If you put it on with no

debridement, I don't know the answer, but I believe it may increase benefit. But certainly, we need to educate the world that debridement is important treatment of a diabetic ulcer, with or without PDGF.

MR. McGUIRE: Dr. Steed, while you're still on your feet, do you have data like this for the next study, for the K Study?

MR. STEED: I do not. Jan Smiell might answer that, but I don't have those data.

MS. SMIELL: I'll address that.

MR. McGUIRE: Thank you.

Dr. Rosenberg had the next question.

MR. ROSENBERG: I was just going to ask Dr. Miller what his recurrence rate would be at that number in his clinic.

MR. McGUIRE: I can't --

MS. SMIELL: Could you repeat the question?

MR. McGUIRE: The question was --

MR. ROSENBERG: I asked what the recurrence rate would be for healed ulcers at the Geisinger Clinic.

MR. F. MILLER: The recurrence rate for healed ulcers, I would suspect it is somewhere around 30 percent.

MR. ROSENBERG: And in that time frame?

MR. F. MILLER: No, I can't say within the time frame. I'm talking about long-term follow-up. I don't have that data at --

MR. ROSENBERG: This is rather quick, you know, just what everybody else is saying. The magnitude of change, depending on who does it, seems to be so much larger than the product in this case -- you wonder. I mean, these were -- when we were told that they could not confirm the 30 microgram efficacy, you know, my reaction is -- you know, I would -- after hearing this this morning, you know, I'd put Dr. Steed's clinic up ahead of whoever did the K Study. And you just wonder about -- within Dr. Steed's study, the 30 micrograms were good, but that's being discounted here now because of the K Study, on which everything else depends.

But in a setting in which how the wound is cared for is of such extraordinary importance, I just wonder how -- what we know about the K Study investigators, and how many were there and how did they do it and how were they chosen, and how would they compare, as has been suggested, with practicing office physicians.

MR. McGUIRE: Who would like to respond to that?

MS. COELLN: Jan.

MS. SMIELL: These were twenty-three investigators, of various specialties. A handful of them came from the F Study, but certainly the minority. We added podiatry, we added more internal medicine. We did have one internal medicine subspecialist, a diabetologist, in the F Study. And we had other surgeons represented: orthopedics, vascular, general. We also had emergency medicine represented.

In general, not all of them that are investigators in these trials make, as a big part of their practice, wound care, but they do see a significant number of diabetic ulcer patients, and were able to enroll a significant number during the treatment periods.

MR. McGUIRE: Bill, is that -- did you have your question answered, Bill?

MR. ROSENBERG: Well, my question was really why -- to what degree do we want to pay attention to the F Study and the K Study? Again --

MS. SMIELL: I think the F Study did show us that becaplermin is efficacious, and what

the K Study did was take it into a real-world situation.

MR. McGUIRE: Mrs. Cohen, you had the next question.

MS. COHEN: Yes. I'd like to talk about the real world, if I may. I would suspect that if this is marketed, everybody who has an M.D. by their name is going to prescribe it. Are they going to do -- be able to do debridement? Are they going to be able to spend the time, now that we're dealing with HMOs and they can only spend so many units with patients? And if some is good, will more be better?

And as far as I can determine, the clinical trials were done at optimum circumstances, and I think, conversely, it should be in some of the worst circumstances, and find out exactly what will happen if 30 microgram or 100 microgram -- who knows what a patient is going to put on? It says, "thin film"; I think that's what they talked about.

So I have a lot of concerns in terms of who's going to prescribe it and who's going to follow through and who's going to do debridement.

MR. McGUIRE: I'm sure the sponsor has the same concerns. Did you want to respond to

that Dr. Steed?

MR. STEED: Yes, I agree, and I have similar concerns about what happens when you go out to the real world. But whether or not we use PDGF, we still need debridement. That's part of good care. Fred Miller talked about that right from the word go. And we need to educate physicians of all disciplines about the importance of good wound care. And if you're a primary care doc and you don't perform debridement, you need to get in touch with your surgical colleagues, dermatologic, podiatric, or general surgical, and have them available to debride, because it is important. So I don't believe that's a PDGF issue, I believe that's a good care issue.

And I'm actually proud that they -- that there's an educational program associated with this product, because we really need to educate people on how to treat the diabetic foot ulcer.

MS. COELLN: I'll add to that by saying that in the proposed labeling we do describe debridement and try to give an explanation or description of what good debridement is.

MR. McGUIRE: Dr. Wilson, then Dr. Harkless.

MR. WILSON: I agree that -- or addressing the question of efficacy, the appropriate comparison is the vehicle versus the drug, and my question doesn't relate to that.

But I am curious that in the studies that had a standard treatment arm, and I think I'm thinking of Study 001, the vehicle was substantially better than the standard treatment. And I'm just wondering if there was anything in the study design or anything in the way the patients were treated or whatever that might be able to explain this difference.

MS. COELLN: One might suspect that the use of --

MR. McGUIRE: Excuse me; I just want to put a friendly amendment onto your question to save me from asking it later, and that is, I wonder if the bacteriostatic or the preservative is changing the microbiology of the wound.

MS. COELLN: I'll try to address both of those, and I'll ask Dr. Smiell to try to assist me.

We believe that there's -- there are some properties related to the gel that would allow the wound to stay moist, and may have had some

beneficial effect beyond saline-soaked gauze dressings.

And regarding the preservatives, we don't have any data to support that there might be a -- any kind of bacterial effect in the wounds.

I think Dr. Smiell may have more to add.

MS. SMIELL: The only thing I'd have in addition to that again goes back to that definition of "infection control." Because in that standard care arm, we did see a higher number of wound infections during that treatment course, and that may have influenced that outcome, as well.

MR. McGUIRE: Dr. Harkless and then Dr. Miller.

MR. HARKLESS: Dr. Rosenberg raised the question about recurrence. And if you look at data, it suggest that there's a 25 to 50 percent recurrence rate of ulcerations. And I have a question on the time to heal, also. What now? And basically, I think you have to link the risk factor structure function, lifestyle, and activity level, as reasons that it also will recur. And I wanted to add that to the equation.

MR. McGUIRE: Okay. Dr. Miller?

MR. C. MILLER: I have several questions. I think they relate back to that slide No. 25 or whatever it was, where you were looking at the incidence of closure and you were looking at the size of the wound. It begins -- my questions begin with the inconsistency of the definition of ulcer staging in the use of diabetic ulcers and in the use -- in the context of a pressure ulcer. Those definitions are not -- not even close.

And it goes on to say that -- I don't think -- I'll change that; I do think there's a difference between "closed" and "closure." And when you tell me it's a percent or rate of closure, that does not imply that it's closed. Now, if you want to tell me the percent of closed ulcers, then I'll buy that slide up there. But in fact, people are showing that because of problems with the definitions of staging, I doubt seriously that you can regress in a staging system of nomenclature or description. So you need to go back to something like healing, described as a percent or rate of healing, or a percent of closure, so -- and your tables, et cetera, would go on, but now you would look at some kind of volume change, with a dimensional adjustment in the planimeter distance

around that wound itself.

So I have real serious problems with the basic unit of measurement that you're using.

That's further complicated by things where we acknowledge a set of fifteen or more co-factors that affect a very complicated healing process. You identified four or five that were, in fact, different. And then the FDA called -- came to the conclusion that if you don't want to use those co-factors to adjust your statistical model, then the best thing to do is to run an intent-to-treat analysis. That's absolutely foolishness.

So I don't believe that analysis has an appropriate -- I don't know for sure whether or not this is much more effective than it's being portrayed to be, or if it's less effective. But I do know that if you come along and tell me that if I adjust for infection, that the treatment effect does no longer exist, which the FDA said a few minutes ago, I better start looking at co-factors and co-variant analysis, or I'm in big, big-time trouble.

Now, I think there's serious problems with the analysis and the conclusions that are being drawn. Thank you.

MR. McGUIRE: Could we have a --

MS. SMIELL: Can I address that?

MR. McGUIRE: Yes, please.

MS. SMIELL: Okay. Slide No. 26 in my presentation was the one with the logistic regression modeling.

MR. C. MILLER: Yes.

MS. SMIELL: Keep in mind, in no case did we show a percent of ulcer closure. What we were looking at were the percents of -- or the percent of the population that had complete closure or complete healing.

MR. C. MILLER: True; I understand.

MS. SMIELL: Okay. And I agree that volume is the best measure for looking at healing rates when you want to do relative ulcer volumes -- that is the best way to look at it.

However, we did not do an accurate volume measurement in the studies. We only looked at baseline -- I mean, at ulcer areas, length times width, as well as planimetry. So you don't have the same accuracy as the three-dimensional volume, which you need to compare healing rates.

This again is the estimated incidence of complete healing in the population.

MR. C. MILLER: Now, excuse me. Are you saying that your clinicians brought their patients in on a weekly or biweekly basis, looked at them, and did not make a clinical note of the size of those ulcers?

MS. SMIELL: Yes, they measured the depth, but it was a crude measurement with a cotton swab. And they measured the length times width, and they also documented certain other characteristics: signs of infection, and in some studies the quality of granulation tissue, and other factors like that.

MS. COELLN: At each visit they also had traced the ulcer, and that's the size that's based on the planimetry.

MR. C. MILLER: Those don't sound like crude measurements to me, if you trace the ulcer --

MS. SMIELL: No.

MR. C. MILLER: -- or if you measure the depth or if you looked at the -- and it's not a big-time mathematical formulation to figure out a good estimate of what that is.

I'm sorry, I'm not trying to be argumentative.

MS. SMIELL: Okay.

MR. C. MILLER: I'm just trying to say what, it seems to me, are some very difficult things --

MS. SMIELL: Okay.

MR. C. MILLER: -- are circumvented here, and we can't develop a positive -- not a positive, a definite position about efficacy.

MS. SMIELL: The point about infection control is a good one. And actually, if you look at it in a different manner for that Phase 2 trial, where you look at the 100 percent healing or complete closure of ulcers within the group that did not have adequate infection control, you still see a significant separation between the vehicle group and the treated group, the 30 microgram group. There still is a 19 percent separation. So while you might lose some significance in the p-value, mainly because of the size of the study, you still see a significant difference in both the not adequately controlled and the adequately controlled, as you see on this overhead.

MR. C. MILLER: We saw the very last slide you put up, where you were talking -- we saw a graphic, classical effect of a co-factor.

MS. SMIELL: Yes.

MR. C. MILLER: And if we can see that there, and we can look at issues like this, then I think those things ought to be built into your model, and not just discard that information. And I think you'd have a much cleaner inference that could be made.

MS. SMIELL: We did do several models with co-factors, with co-variables. However, we weren't able to put all fourteen into one model.

MR. C. MILLER: That was never clear to me, why.

MS. SMIELL: I think Dr. Perry might better address that.

MR. C. MILLER: Or at least a model with those that were shown individually to be significant.

MS. PERRY: I'll try to address your question with how we handled the co-variants and what we did. We examined all fifteen of those co-variants in our logistic regression model. And what we found was that in all instances the primary contrast of interest, which was becaplermin 100 microgram to vehicle, remained significant. In the presence of those co-variants or without those co-variants, the conclusion was the same.

In the one instance, which was in the F Study, where we did see a change in the p-value, the p-value, yes, changed, but that only served to highlight the importance of good wound care, and specifically infection control.

MS. COELLN: I think Dr. Robson also has something he'd like to add to this discussion.

MR. ROBSON: Dr. Miller, I agree with a lot of what you said, and I want to suggest some inconsistencies between this and the problems with the Agency.

We've done a lot of studies where we've looked at volume decrease over time. And if it doesn't get to zero, the patient still has a wound. And therefore, in a combined meeting with the Agency and the NIH and the Wound Healing Society, they came to the conclusion it had to be closed, as you said.

And therefore, the end point on this was that it was 100 percent healed, or closed. And I think that makes a big difference, because we're now down, depending on whose numbers you look at, to somewhere between 7 and 10 percent difference.

And I'd like to go back to the original numbers. If that's 2.4 million people,

that's between 160,000 and 240,000 patients who no longer have a diabetic ulcer because of the use of this, added to their other treatment, however good or bad it may be, depending on where they're being treated. And I think that's very important.

MR. C. MILLER: I hope you noticed that I left the door open, because I don't know how effective or non-effective that is. I don't have an estimate of what your product can do. But I do understand that it looks beneficial. It looks beneficial. It looks like analysis could show a lot more efficacy than it is. But I think we're a minute away from HCFA telling us there's a limitation on almost all kinds of care. And when that happens, efficacy and cost-efficiency will, in fact, play a part in that.

So I'm advocating a different end point, and I think at least we use concomitantly with this.

MR. McGUIRE: Okay, we're going to have one last remark from Dr. Mustoe.

Dr. Miller, never apologize before lunch for being argumentative. We have the whole afternoon coming.

MR. C. MILLER: Well, we'll make them

look at it.

MR. McGUIRE: Dr. Mustoe?

MR. MUSTOE: I don't know how long this will take, but the -- so -- but I have seen very little discussion of the 002 Study, which was, in fact, a very large study with 125 patients, as many patients in the treatment arm in that study as your pivotal study. You saw lack of a treatment effect, at least lack of a statistical benefit. You made some discussion of that.

But one of the things that concerns me is the possibility that in that study, again, you have an even less educated group of wound care specialists, and so the reason you lost effect was in an even less effective utilization. And unfortunately, if we carried that out to the community, we may not see a benefit of PDGF, if that is in fact the case.

And I guess I would like to hear a greater elaboration of why you feel that that -- I mean, have you excluded that possibility by, for instance, analysis of the frequency of debridement or some other ways to analyze why -- why you didn't see a treatment effect in that very large study?

MS. SMIELL: Okay, the -- when we now

-- when we analyzed the factors that affect healing, the one that -- two of them -- actually three in the study were important. Baseline ulcer area, as we mentioned, across all trials was important, and also the protocol compliance. And protocol compliance is really the evaluable for efficacy criteria that were set forth in the analysis plans for the individual trials prior to doing -- getting all of the data cleaned and evaluated. And this is an example where, if you look at --

The population with the most consistent response is that less than or equal to 5 square centimeters. And remember, they were allowed to enter ulcers up to 40 square centimeters in this study. And also taking into account those who were protocol-compliant, this would exclude people who did not fit the entry criteria, who didn't come in for their study visits -- they were allowed to miss a maximum of three study visits throughout the course of fourteen visits -- and they weren't compliant with a non-weight-bearing regimen. These were all the factors that were taken into consideration with protocol compliance. And what you actually see here is that that study gains significance, a significant difference, of 33

percent versus 45 percent in vehicle to becaplermin.

MR. MUSTOE: So in essence, that does tend to support the hypothesis that in that study there was an unusual number of non-compliant patients. Perhaps you could also say that might mean that the investigators were the least committed or the least skilled, and that if you carry this community, that could still be a problem, that you could have a washout of lack of benefit because of lack of compliance.

MS. SMIELL: Well, one of the other problems in this study is, there's an imbalance in the smallest ulcer sizes as well, which may have increased the efficacy of our standard care, and given an unfair advantage to that group, compared to all the other studies.

MR. C. MILLER: Could I have thirty seconds before we close?

MR. McGUIRE: Would it wait until after lunch? I'd like to -- I'd like to declare that it's lunchtime, and come back here at 1:30. I mean, everyone has lots of questions.

(Whereupon, luncheon recess was taken at 12:34 p.m. until 1:34 p.m.)

MR. McGUIRE: Good afternoon.

The Agency has prepared a set of interesting and complex questions for the Advisory Committee. We have a -- we have a complicated series of questions to deal with this afternoon.

First, is there anyone from the public who has -- is on the schedule this afternoon?

I see no one, so we'll go on to the open Committee discussion.

The first question posed to us --

MS. BERGFELD: Are there any other open questions? I mean, questions from the panel that we --

MR. McGUIRE: We'll fold those in; otherwise, we'll go on.

MS. BERGFELD: Okay.

(Pause.)

AGENCY QUESTIONS FOR THE COMMITTEE

MR. McGUIRE: Question 1 is the consistency of efficacy results.

All of the Advisory -- each of the Advisory Committee has your questions:

"Variability of about 10 percent in absolute difference was observed in the incidence of complete healing in similar treatment arms across the four efficacy trials. The explanation for this

lack of consistency likely reflects aspects of trial design and/or conduct.

"It is important in planning the trial to consider" -- "to carefully consider use of controls, standard care or placebo, blinding techniques, double-blinding or third-party blinding, enrollment criteria that determine the heterogeneity of study subjects with respect to co-variants and co-morbidities -- that is, ulcer location, stage, duration, area at baseline, periulcer TCPO2, the nutritional status, organ dysfunction, and so forth -- that affect ulcer healing.

"With regard to trial conduct, variations of standard of care, including infection control, debridement type and frequency, non-weight-bearing compliance and methods, and patient glycemic control also influence ulcer healing.

"Please discuss which of the co-variants mentioned above are most critical in healing diabetic neuropathic ulcers.

"Please discuss what mechanisms might be used to address these important co-variables by stratification or by co-variant analyses.

"To what extent might more consistent trial design conduct be used to control

variability?"

And then there's a second part to that question, but this is sufficiently complex that I would like to deal with it first. Would anyone from the panel like to open the discussion?

MR. ROSENBERG: Well, I would.

MR. McGUIRE: Dr. Rosenberg.

MR. ROSENBERG: I think this is the kind of thing that can happen when one draws conclusions from studies that were designed to test something else. It's certainly taught, and we all recognize that if you're doing a study to look for something and something else emerges, you must not ignore it; it's frequently more important than what you were studying. Nor, however, can one draw conclusions based on those observations; one should then do a further study designed to test that.

And this morning and in our booklets to take home, you know, we've seen one study done with a 30 microgram product, which is now no longer considered, one study that was a Phase 2 safety trial where some material was put in to improve patient compliance, and the observation was made, although not really looked for in the sense of a stratification of patients, one which was a quality

of life study without the double -- without the double -- without the placebo. So we're really left with the K Study, it seems to me, as the one study here.

And considering how important this is -- I mean, this is of immense importance. It would be dreadful to walk away from something that can help people with diabetic ulcers, and miss it because of objections to the way the data came in.

But a market this large, it strikes me, deserves the kind of studies that one expects when one is looking for answers to limited questions.

And there's just one other question that I just want to raise, another member and I were talking about. One of the things that -- of course it's so dreadful, this amputation of diabetic limbs, but we haven't -- I don't know; it would be nice if somebody told us to what degree amputation correlates with these kinds of neurotropic ulcers, to what degree amputation versus vascular -- to what degree amputation correlates with ulcers less than 5 centimeters in diameter, which are the ones in which this seems to work, as compared to larger ulcers, and to what degree, based on what we know about the

dreadful problems of diabetic legs, something that had this percentage of effect on well-debrided small neurotropic ulcers would play a meaningful role.

MR. McGUIRE: Okay. Yes, Dr. Lipsky?

MR. LIPSKY: I can address this in part. I'm sure Larry Harkless can address it further, some of the questions you've raised, Dr. Rosenberg.

As you've heard, most of the ulcers diabetics get on their feet are, in fact, on a neurological basis rather than a vascular basis. The ones that occur on a vascular basis are usually fairly easy to pick up and are treated with, nowadays, vascular bypass in centers that can do that. And those patients usually don't go on to develop a -- to have a need for amputation. Those persons who can't have that procedure, who develop vascular ulcers, probably are at even higher risk for amputation than patients who have neuropathic ulcers.

The pathway from ulcer to amputation has been well defined by Pecoraro and others in a classic paper that looked at patients who went on to amputation, and tried to figure out what was the initial event and what were all the co-variant

events that occurred, and infection was responsible for at least 27 percent of those. And the most important thing was developing a neuropathic ulcer. So it's probably the most important single event, or it's the pathway that ultimately leads to amputation.

I think the other key feature is not only whether or not you completely heal more ulcers with one therapy versus another, but the rate at which those ulcers heal. Because every day that that wound is open leaves it at risk for infection, as well as puts the burden on the patient and his family of dressing that wound and being somewhat less able to do the things that they might otherwise want to do. So I think there are a number of issues that you raised that are of importance.

I'll let others comment on that, but I'd like to come back with a different question when you think it's appropriate.

MR. McGUIRE: Okay. Are there other comments to Dr. Rosenberg's questions? Dr. Hashimoto.

MR. HASHIMOTO: Well, this morning we saw at least three times of diabetic ulcer. One is ischemic type, another one neuropathic, and this

study seems to be concentrating neuropathic variety, but also bone deformities mentioned. I think the different type of ulcer we're dealing with, that's one of the major causes of this variability. I just wonder if we take a biopsy or something to obtain initial stage, evaluate fibrosis, vascularity, or even non-invasive Doppler measurement of the circulation, some kind of uniformity at entrance will make the study population more uniform.

MR. McGUIRE: I think some of the criteria that were mentioned this morning were the ABI and the neurologic examination, duration of the ulcer, location of the ulcer. The question has been raised as to whether biopsy is -- would be a useful adjunct, and perhaps it would. I think -- I think that for people who deal with diabetic ulcers, they're stereotypic enough that one could make the clinical diagnosis based on a handful of criteria. But that should be discussed further.

Dr. Lipsky, you had a second part to your response.

MR. LIPSKY: Yes. My chief concern about this issue is what would be the potential adverse effect of this product if someone who is currently practicing proper wound care -- that is to

say, with debridement -- were to substitute this for that proper wound care. That is the one instance in which I can conceive that the addition of another product that's potentially beneficial, even if it's only 10 or 15 percent better than what's currently available, were to be put on the market. I think it's worth thinking about that.

If you are based in an HMO with a certain number of minutes per patient, and you say, "Well, I know debridement's the way to go, but here's a new product that, in fact, appears to be quite effective, and maybe we can try using this rather than going through that laborious process" -- there's no reason to think *a priori* that somebody who is already doing the right wound care -- that is to say, doing debridement -- would abandon that, because any of us who do it quickly recognize it's the most important aspect in the start of the care of the wound. But that would be, to me, the only instance in which I could conceive that introducing this product, as we've heard about it to date, anyway, would potentially have a negative impact.

MR. McGUIRE: I think -- I hope I didn't imagine this, but I think what I heard this morning is that the sponsor is aware of that.

And we also -- I tried to avoid a discussion about health care financing and HMOs, but the -- there will be a balance struck. And if it's a question of using a health provider's time or buying an expensive product, I expect it's the providers who will be doing debridement. But that -- I think should be clearly stated. And we all should be aware of it, that there is a potential downside if someone sees this as a panacea that replaces other more difficult and tedious forms of high-quality care. It's a good point, but I think it's well understood on both sides.

Dr. Lavin?

MR. LAVIN: I'd like to make a couple of points relating to, I guess, the core of this question, which is the issue of --

MR. McGUIRE: Move a little closer to the microphone.

MR. LAVIN: A couple of points here. First off, one of the things that surprised me considerably here was that the vehicle has, you know, efficacy over a wider range of ulcer sizes. In the logistic regression analysis that was displayed this morning, that I'm supportive of, I think that analysis demonstrated that the vehicle

efficacy, you know, went up to 4, 5 square centimeters; whereas for the standardized care, that efficacy, you know, appeared to drop -- from what they drew on the board there, it appeared to drop off at around 2, you know, square centimeters. And I think that that will have an impact on any kind of a design that you do.

I think it makes the results very difficult to interpret. And the comparison to a vehicle control, in a sense, becomes the more difficult challenge. And here they are, in Study F, here they are in Study K demonstrating significant advantage over -- you know, over vehicle, which is the more difficult comparator in a true clinical trial, you know, setting.

So I think maybe I would just ask the sponsor if they happen to have any data that would show the effect of size on standards -- on the standard care, just to be able to give us some sense of what that variability is. Because I think that's a point that will bear on the discussion tomorrow, as well as the discussion the rest of the day.

MR. McGUIRE: Phil, you're asking the effect of vehicle *vis-a-vis* the size of ulcer and also standard care *vis-a-vis* ulcer size.

MR. LAVIN: Right.

MS. SMIELL: This is a logistic regression model for the one square centimeter group, the group that was in common across all trials, which also includes the standard care arm in the studies, the four trials. That's this arm right here.

As mentioned, there is interaction in the very small ulcer sizes. And this, I think, addresses your concern, Dr. Lavin, that this may be an unfair comparison because of this.

MR. LAVIN: Maybe you could show the other two, the other two slides which you referred to as well, that show the effect of standard care through the individual studies, just to be able to see how Study 002 did.

MS. SMIELL: That's the individual study centimeter by centimeter. We don't have the model for individual studies, but we have the centimeter by centimeter plot.

This is the same study to which you were referring, the DBFT-002, where you see a propensity of small ulcers in the comparator group, and you see a pretty consistent efficacy over the entire range for the becaplermin group. But because

of these, it sort of wipes out the benefits seen here.

The other study, DBFT-001 -- I think it's No. 83 -- 81; sorry, wrong direction. This is the other study that has the standard of care group. And what you see here is basically, again, a pretty consistent response for becaplermin over the standard care group. In this case the -- I'm sorry; standard therapy is purple and vehicle is yellow.

MR. LAVIN: And I think just to sort of hammer home a point, I think that basically means the studies with vehicle are going to be more critical, so that puts emphasis on Studies F and Studies K as the ones for the judgment of efficacy.

And my sense with Study K is, what they did is, they basically chose a different dose, because they had clinical data. That was mentioned this morning, and that is fair game. And they statistically went about that fairly to look at the -- to test the 100 does before they tested the 30 dose. So they properly set up the trial, they did it up front, *a priori*, so there really wasn't any of this "back into the analysis, do it backwards." They really did it the right way, properly statistically.

MR. McGUIRE: Yes.

MS. WEISS: I just want to comment that in discussions with the sponsor regarding the K Study, the initial idea was that there's going to be a Bonforoni adjustment looking at both the 30 and the 100 microgram.

And then subsequently in discussions before the trial was completed and the analyses were done, we had discussions with the sponsor regarding modifications to that plan, where it was changed to be the step-down approach, looking at efficacy of 100 first. So there was -- certainly at the time the trial was initially proposed, I think there was probably some thought that the 30 microgram would also be efficacious in a statistically significant sort of manner. But as you see, the results are what they are, and the analysis was the step-down approach.

MR. McGUIRE: Dr. Miller?

MR. C. MILLER: Thank you. I feel like we have a mixed bag here of logic. And I concur that if there is a population out there that can profit by this treatment, we certainly should not neglect them. And I would be more willing to compromise statistical theory than I would the

opportunity to help those patients.

On the other hand, for consistency, we have a study that was designed to admit all of these patients based upon a non-healing duration. It didn't say that we were going to analyze or specify the utility or efficacy of this drug or this product based on size of the -- of the wound. So it seems to me that that's one point of view.

When later on in our discussion we come around to the fact that we can't do an analysis adjusting for those co-variants, which we would have known existed had we looked at the literature very, very carefully -- we can't do a co-variants analysis to look at effects and to adjust the effect, because is was a *post hoc* proposal for analysis.

Now, in one case we're not sticking to the admitted people who were intended to treat, we're knocking it down to less than 10 centimeters, and on the other side we're saying we can't find out the real effect because we can't plug those in, or that we can't look at a different concurrent, at least, end point. Now, to me, that's not consistent.

I would like to see us consider an analysis -- now, I've talked to them, as I

understand inappropriately, during the break. And those analyses were done. Some of those were done. And it seems to me like, with this inconsistency, that there is a justification for the sponsor to tell us more about how those co-factors did, in fact, affect the end points, so that we have a better idea of what range this thing really is effective.

MR. McGUIRE: Dr. Coelln, would you or anyone like to respond to that?

MS. COELLN: Dr. Miller, could you give us a little more specifics on what you'd like us to present?

MR. C. MILLER: Well, I understand that there were four or more co-factors -- for example, like our infection, that when we controlled for that, it altered our assessment of the efficacy of that product. Now, if there are three or four others, I don't know if they go up or if they go down or what happens when they're considered concurrently. But my guess is, we're going to do a better job.

And I also would like to know what the analysis will look like when we truly look at rate of healing, not rate of closed. I think we

might see different things.

MS. COELLN: Dr. Perry, if you'll address that --

MR. C. MILLER: Now, maybe that's some -- by the way, I wouldn't expect you to have that right here, but if you do, I'd like to hear about it. And if not, maybe perhaps FDA could hear about it at a later date.

MR. McGUIRE: If I may, let me see if I understand the second part of your question.

We're again back to the number of wounds that were closed versus the other kind of data, which is the rate of closure.

MR. C. MILLER: That's one of the things --

MR. McGUIRE: That is your second point.

MR. C. MILLER: -- that needs to be straightened out.

The other one is the logic of making your labeling associated and appropriate only for 10 centimeters or less. I think that that's -- since the intent to treat was originally for everyone, based upon a time window, not on a size window, then it seems to me like that's a *post hoc* decision about

efficacy. And I feel like if you're justified in doing that *post hoc*, you're justified in looking at alternative end points in looking at the effectiveness.

MR. McGUIRE: Okay. That's a fair question. But there's nothing wrong with learning something from the clinical trials.

MR. C. MILLER: Right.

MR. McGUIRE: Okay.

MR. C. MILLER: Right.

MR. McGUIRE: So let's hear from the sponsor.

MS. COELLN: Okay. Perhaps, you know, we don't need to be limiting the population to the less than or equal to 10. But since this was the first really large database available, we did feel it was important to evaluate that data, and we did see the most consistent efficacy in that population because, of course, that is the majority of the population.

Perhaps, Dr. Perry, do you have anything to add to that?

MS. PERRY: I can only remind the Committee that of the fifteen co-variants we examined, we paid close attention to the behavior of

the key contrast of importance, comparing becaplermin 100 microgram to the vehicle. And in those analyses sometimes the p-value would go up a bit, sometimes it would go down a bit, as you would expect when you start looking at lots of co-variables. But our conclusion never changed, and we never lost the significance of 100 compared to vehicle.

MR. McGUIRE: Dr. Rosenberg?

MR. ROSENBERG: Getting back to the size, I think the second transparency we saw this afternoon had to do with size.

MS. PERRY: Yes, that's the --

MR. ROSENBERG: It was the green and the yellow bars.

MS. PERRY: Yes.

MR. ROSENBERG: The size of baseline ulcers.

MS. PERRY: Yes, that was in the DBFT-002 Study.

MR. ROSENBERG: Could we see that again?

It looks to me like for the very small ones -- well, the one to two -- in other words, this is telling us -- as you go all the way

up to -- it looks like to two -- I mean, your -- the main -- the active is better on these tiny ones, which seem to be less than one, which is -- and then one to two, the standard seems to be better. And then at two to four, the product seems to be better. And you know, all these things are perhaps explainable.

I just had a question about diabetic ulcers, two questions I would like to ask those who treat them. One is the relative population of ulcers, where they hit on that zero to one, one to two, et cetera.

And secondly, those in whom the dreaded complication of amputation arises, where are they on size? Because the data indicated that larger than 5, you didn't have -- it wasn't just larger than 10.

MR. McGUIRE: Yes.

MR. F. MILLER: The question of amputation has been raised before. The lesions -- in the best treatment scenario, the patients who go to amputation are those patients with ischemic disease, in whom there cannot be revascularization for whatever reason.

The second group that might lose a

limb would be those who have a mixed disease, neuropathic and ischemic disease, and again cannot be corrected.

It might be somewhat of an overstatement, but I think that if patients have pulses and if they are strictly neuropathic, they should not come to amputation. Now, the ones who might, would be those who have Charcot feet with just horrendous deformities, into which you cannot find a show to fit them. But generally, if patients have pulses, amputations should be avoided, because you should be able to avoid the infection.

Patients whom we see are those who have lost a toe because, quote, "it didn't heal." But why didn't it heal? You know, how was it treated? And then another toe, and then you begin to get new pressure points, new ulcers, and they will go on to amputation. The ulcers that we see -- you know, again I'm trying to pull it out of my own head here -- probably 2 to 3 centimeters diameter, the majority. And which ones would go on to amputation? The ones that might be very, very large when they come in, you know, where they have an ulcer that's burrowing through the -- through the foot. Does that answer your question?

MR. ROSENBERG: What I'm trying to get at is, assuming that this material is as effective as the one study, the K Study, seemed to show, how many -- what percentage of amputations could be obviated?

MR. F. MILLER: Well, again I go back to my first point. And I think if you have a neuropathic foot with good ulcer -- with good pulses, they should all be obviated.

MR. ROSENBERG: Okay. Thank you.

MR. McGUIRE: Do you want to finish? You want to finish up?

MR. F. MILLER: Yeah, I wanted to ask a question along with that.

MR. McGUIRE: Okay, go ahead, Dr. Miller.

MR. F. MILLER: And this is to the sponsors. We looked at the groups of people in the studies, and we have leg ulcers, we have four foot ulcers, and we have heel ulcers. And my question would be, what types of neuropathic leg ulcers are seen, and my second question would be, with the forefoot ulcers, which ones were metatarsal heads? What percentage were metatarsal heads, and what percentage were toes?

And then if you look at your data with the healing, were the metatarsal head and the heel lesions, which are the most difficult to treat because they're the ones that you must off-load and they're the ones that we usually have contact casting or some other type of orthotic mechanism to relieve the pressure -- did you see healing in those people? Because the time frame for the healing was, you know, twelve weeks, I think. And you know, that's a relatively long time; that's three months. And for those ulcers which might be on a toe or on the dorsal part of a foot or on an ankle, that would seem, to me, to be quite long.

MS. SMIELL: Okay. First of all, 73 percent were forefoot, which does include the toes and the metatarsal heads. About 23 percent of the overall population of ulcers were metatarsal heads. The leg ulcers that were seen were the smaller percentage, but did the best. And those typically were ulcers on the malleoli.

We have a slide that shows the split, if you'd like to put that up, S8.

The healing was best in the leg ulcers. Here we go. This gives you the percentage of ulcers of the overall population, by not only

foot versus leg -- and you see only 6 to 7 percent are leg -- but also plantar versus dorsal, plantar for the majority of them, 50 percent toes, and this includes both plantar and dorsal toes, metatarsal heads 20 to 25 percent, and the heel is what, 8 to 9 percent. I don't have it separate, the healing rates specifically by these regions, except to say that it was best in legs, second best in metatarsal head, and worse in the heel and arch regions, which make up other locations of the foot.

MR. F. MILLER: How about the toes? Where does that fall? Where do they fall?

MS. SMIELL: Well, the toes were combined with the metatarsal heads in the forefoot location. And that's where we have -- most of the healing rates you saw today are consistent with that.

MR. F. MILLER: I would just comment that with toe ulcers, for example, dorsal toe -- the toe ulcers usually result from the anatomy: you know, you have a claw toe or you have a hammer toe. So that you might see it on the dorsal toe or you might see it on a toe pad, because it's constantly hitting the bottom of the shoe. And on those, you know, we'll rupture an extensor or a flexor tendon

to straighten out the toe, and then they usually, you know, heal pretty readily. So I think that there's a very distinct difference between toe and metatarsal head ulcers in the ease with which you can treat them with standard, you know, therapy.

MR. HARKLESS: My question -- I have a question. Did you stratify the differences in the distal toe versus the interdigital area, or dorsal?

MS. SMIELL: I apologize; I can't hear you.

MR. HARKLESS: I said did you stratify the differences between the distal pad of the toe, the distal end of the toe, the plantar pulp, versus interdigitally or dorsally?

MS. SMIELL: No.

MR. HARKLESS: Because I would expect to see a difference in the healing rates in those particular ulcerations, just by location and the bony prominences.

MS. SMIELL: No, we did not.

MR. McGUIRE: Okay. Dr. Steed?

DR. STEED: Yes, I'd like to make a comment on amputation and what percentage of patients could be saved. I'm a vascular surgeon, and when a patient comes to me with an ulcer, I

sometimes think it's better to be an ischemic ulcer, because there is an accepted treatment which works, which is revascularization. And if they have an ischemic ulcer and you revascularize the foot successfully, they almost always get better. And the patency rate for distal bypass in diabetic foot ulcers at one year is 90 percent or so. Most of them have very distal disease at the tibial level, and bypass, in situ bypass with inflow at the level at the knee and outflow in the foot -- Frank LoGerfo has shown that the patency rates at one year are over 90 percent, and at three years are over 80 percent. So I might argue that in some respects those are easier ulcers to treat.

And we do have those patients who come to amputation, but we also have two other common scenarios.

One is a patient who has an ulcer on a toe or under a metatarsal head; the ulcer becomes -- I think it's not so much the location, but whether or not it burrows deeply. If it goes into the joint space or involves a tendon sheath and we can't get it better, the patient comes to an amputation of the toe. Then the toe amputation site doesn't heal, you keep whittling back, and the next

thing, it becomes two toes, all five toes, or higher.

The other scenario is, they have an ulcer and they have pus which tracks along the plantar surface or along the tissue planes, and the next thing you know is, you have pus throughout the foot. And we have done a number of amputations on patients who have a palpable pulse, or certainly have a good Doppler signal.

So I think it's a mixed bag. I think patients do come to amputation for both reasons.

MR. McGUIRE: Dr. Margolis?

MR. MARGOLIS: Yes; to Dr. Miller's point just a second ago, in the book that we were given called BLA96-1408, on page 38 there is a discussion of what are either univariate or bivariate logistic adjustments for higher baseline albumin, higher baseline TCPO2, compliance with non-weight-bearing in all sorts of non-weight-bearing locations, all being associated with better healing, and ulcers of longer duration, greater baseline ulcer depth were associated with reduced healing. So obviously, you either did univariate or bivariate analysis for each one of those points.

And I just ask this question again:

were all of these co-variants ever forced into the logistic equation at the same time to see how that influenced your estimated outcome for your agent versus vehicle?

MS. COELLN: I believe Dr. Perry will address that question.

MS. PERRY: No, we did not prepare a combined model of these variables; we thought it best to look at them singly.

MR. McGUIRE: Dr. Harkless?

MR. HARKLESS: I want to comment about Dr. Miller's comments. The most common reason that I amputate is usually for an infection due to a neuropathic ulcer. And we keep about six patients in the hospital, not counting about five at the VA, all the time. And they will continue to talk on that particular ulcer, so the faster it closes, I would think that it would probably help decrease that particular recurrence rate, if you will.

But it's usually the patient that walks that will get an infection, and because of the delay in treatment due to the loss of protective sensation is why they are there, and that's why it's a difficult problem to correct and why it is a mixed bag.

There is a subset of patients, probably about 10 percent, with ulcerations that will have a palpable pulse, that still will not heal. But that's directly related to the infection. If the infection stays there a lot, it creates significant, massive destruction. And if it's in the planar aspect of the foot, it gets into central spaces. And we tend to wait around a long time before you actually intervene.

If it's the dorsum of the foot, we see a significant increase in staph and strep in that particular area, with the necrotizing cellulitis. I didn't know what that was until about three years ago, but I would say we have at least two or three patients per month that will have an ulceration from an inner space or dorsal area that will enter the fascia planes. And the key to that is all the delay in treatment.

So the ulceration does play a role in our particular amputation rate. It's primarily related to the duration and whether there's intervention appropriately to allow it to be closed, and therefore to remain closed, with appropriate education and intervention strategies.

MR. McGUIRE: Dr. Lipsky?

MR. LIPSKY: Well, not to keep beating the same drum but to return to infection, I still don't completely understand the concept of infection control. As I understood Dr. Smiell's comments, it sounds as if, after the trial, those patients who developed infection were those who were considered not to have infection control, and those who didn't, had infection control. I hope I understood that correctly.

The question I would have is, were the data analyzed looking at patients who received antimicrobials for whatever reason, be it a UTI or pneumonia or for a foot infection, versus those people who did not receive antimicrobials? I would -- I would like to feel comfortable that the effect on wound -- on ulcer healing was the product, rather than an unintended effect of antimicrobial therapy.

MR. McGUIRE: Dr. Smiell?

MS. SMIELL: We did not do the general analysis of all antimicrobials versus healing. We were going to attempt to look at antimicrobials, specifically for the wound and the effect, and we found that in a lot of cases we had prophylactic use. So it was very difficult to judge whether they were related to infection or not, in a

lot of cases, and we didn't do it.

MR. LIPSKY: Well, I can understand that. I guess I would be interested in seeing the data for those who got treated with an antimicrobial for any reason, since you're right that sometimes the -- it's hard to tell why the antibiotic was used, or sometimes it was used for more than one indication in the same patient.

But I think it would be important to know that whether or not the patients received antimicrobials, this product was effective.

If it turns out this product is only effective in the face of antimicrobial activity, that's important to know. Or if it turns out that the majority of the effect is antimicrobial rather than product, that's important to know as well.

MR. McGUIRE: Dr. Wilson, did you have a question a minute ago?

MR. WILSON: No.

MR. McGUIRE: Yes?

MS. WEISS: Could I just go back to -- there's a lot of very interesting discussion just now, but it leaves me just a little bit confused about the specific question that we were posing to the Committee to try to get a handle on, which were

whether or not from this group of experts we can get some appreciation about -- of all the many co-variants that can be evaluated and looked at in any trial, but specifically the type of trials for these kinds of patients that we're talking about today -- whether or not they are very specific co-variants that this panel could identify for us, and for giving advice for future companies that should be -- the ones that are brought to the forefront.

And the second part of that question would be, then how do you use those, those co-variants? Do we look at that in terms of some kind of stratified randomization? Should we do an adjusted analysis?

I think that's the kind of question we're trying to address and the kinds of advice we wanted to get from the Committee about that. It's a difficult one.

MR. McGUIRE: Well, I think the Committee is trying.

MS. WEISS: I appreciate that.

MR. McGUIRE: And what we're -- we're a little confused, "we" being me -- are a little confused about infection and when it's -- when it's

identified.

Some of the -- some of the variables are really criteria for inclusion in the study, PCO2 for instance, and ABI. So you know, some of those have already been -- have already been taken out.

But it sounds like the size of the ulcer is crucial. And where I'm -- where I need some help is whether we're talking about 10 square centimeters or 5 square centimeters. I thought the discussion this morning at the end of the morning was focusing on 5 square centimeters, which is about -- what is it? About 22 millimeters in diameter.

Yes, Dr. Thomas?

MR. THOMAS: Just to address that from the standpoint of doing studies, not only in diabetic wounds but also in other wounds, stratification doesn't -- is not very practical, in the sense that you end up with fewer numbers of each cell, to the point that it just takes forever and gets very complicated.

I think they've done a pretty good job of trying to take out some of these variables in the inclusion/exclusion criteria. There are some variables that we haven't seen, that may be co-variables. And I think the only way that you can

deal with those is to try to force them in the model and see what happens, which is what David is suggesting. And I think you'd want to see that.

That's not critical when there is a huge treatment effect. But when you're talking of a treatment effect of about 10 percent, then it becomes -- baseline characteristics can sway that very, very easily. And so you'd want to look at some co-variables, in terms of descriptions of these populations, of our diabetic control. Some of the things are covered, and covered quite well in the study design. Other things, you know, we don't know a lot about.

MR. McGUIRE: Dr. Lipsky?

MR. LIPSKY: Just to add to that, I would clarify that use or non-use of antimicrobials would be a variable that should always be looked at when you're looking at this issue.

The other variable that, from our perspective in the patients that we see, is important is what the home situation is like. If you ask somebody to go home and dress a wound twice a day and stay off their feet, it implies that there's somebody else who's making meals and doing the other activities that need to be done around the

house, and who can help that person, who often has eye disease and is elderly and otherwise chronically ill, to do the wound care that is necessary for the wound to heal. So some measurement of home support, I think, is an important variable.

MR. McGUIRE: Yes, Dr. Mustoe?

MR. MUSTOE: Yes. I guess I would just follow up on Dr. Thomas, that I do think -- I would also agree that if you stratify too extensively, the groups get too small. But in this study it still concerns me that the toe and metatarsal heads were not broken out separately. And I do think in terms of diabetic ulcers, location is potentially an issue. And the metatarsal head and the heel, where pressure relief is much more difficult to achieve -- I would be more comfortable if a greater effort had -- would be made in the future to specifically try and evaluate how effective the patients are on pressure relief.

And perhaps debridement of calluses is one measure that should be specifically looked at.

But certainly it's very different to say a diabetic ulcer is -- that the treatment's effective in accelerating healing of a -- let's say

a toe that you already expect to heal, versus actually having a high effect on avoiding amputation.

MR. McGUIRE: Dr. Miller had a question. Dr. Miller?

MR. C. MILLER: I want to make two comments. The first of these is in direct response to the FDA's question. That is, the sponsor here has done a very good job of enumerating a number of co-variants that should be and could be considered in the models. But the FDA has added to that list, and certainly literature could add more variants to it.

The issue of whether or not you co-vary it or stratify has been answered fairly well, and that is, it depends on the effect that it has on individual cells that are participating in some kind of a contrast.

What concerns me is that this is proposed to be a project that is looking at the total, I think, care, standard of care. I don't see very many variables in this system that acknowledges that home environment and that support system that was referred to a few moments ago.

Or we have a -- as far as I can see,

a minimum number of observations that address -- or variables that address the issue of consistency. And I feel like that in the future you need to build that into any model that you're going to try, and any design that is going to look at that. The way we talk around here today, it sounds like we're only concerned with the acute process of debridement. But in fact I know that's not true, that you're also following up with those at-home services, et cetera.

So I think those kinds of things need to be looked at very carefully. That environment varies so much, from who's available to help you do it --

MR. McGUIRE: Well, I'm sure -- I'm sure you appreciate that that's the reason that debridement has been emphasized, is because it's easier to measure; we know when we did it. And we don't know what's going on at home all the time, and it's hard to put numbers on things like that. But your point's well taken.

Dr. Lavin?

MR. LAVIN: Just a couple of other points, just to sort of nail down some other variables that are useful here: I would look at hemoglobin A1c, just to see if the, you know,

diabetes is under control; obviously, location of the ulcer, as mentioned already, whether it's weight-bearing; some nutritional measure, something perhaps like serum albumin might be good to look at; also duration of the ulcer that's being treated. And those -- just some other ones as baseline co-variants.

The other variables -- I think we have to sort of keep in mind in doing analyses like these that we have variables that we know at baseline, and we have other variables that occur during the course of treatment. And we really need to look at those, either as time-variant co-variants or look at them as dependent measures. And these would include the use of antibacterials, whether or not the patient was debrided during the study, and also measures of compliance. Because often these variables are outcome measures, and they're more critically and better analyzed that way, or as a time-variant co-variant, than they are as a -- as a predictor of the proportion or the percentage with complete healing.

MR. McGUIRE: Dr. Coelln has some information that bears on your remarks, Dr. Miller.

MS. COELLN: In general, we've been

talking about the use of Regranex in conjunction with good wound care, and it's certainly, as you heard earlier, something that we do certainly understand. Of course, in our trials the product was tested in accordance with good wound care, and there's no -- we have no data to suggest yes or no, whether it works without that.

But to get at the question of patient education as well as good wound care, I have someone from the distributing company who's going to be involved with the education that we will be providing, and I'd like to ask him to come up and present that information.

MR. C. MILLER: We're talking about labeling?

MS. COELLN: No, this is -- this is in addition to the labeling. In the labeling we do indicate very clearly that this product should be used in conjunction with good wound care, and we do describe what debridement is. But in addition to that, because we recognize the importance of this, we are supporting education. And that education is both to physicians and care-givers as well as to patients. And John Johnson can describe what that is.

MR. JOHNSON: First of all, let us say that we do share the Committee's concern about the level of wound care in the use of Regranex. And in fact, education is the single most important element that we view in a successful roll-out of this product in the United States.

Currently, we plan to target education at the families and the patients, education at the physicians who will sit and do the diagnosis initially, as well as education to those physicians that do debridement.

Our plan is to first go out to those physicians that do debridement and educate them on state-of-the-art techniques around debridement, as it relates to everything from videos on debridement -- in fact, we've done at Dr. Steed's clinic which would be rolled out and handed out throughout the United States -- centers of excellence where they could attend to get up to date on current debridement techniques. National, regional, and local symposiums would be funded and are currently planned in conjunction with the roll-out of this, all around debridement and good wound care.

In addition, with the primary care physicians -- and we heard some discussion on that

this morning -- the plan is to really focus on diagnosis. In fact, we partnered with the American Diabetes Association to help expand their foot care screening program. And what we would ask is that once those patients are diagnosed, to send them to those physicians that do debridement and are up to the state of the art.

But importantly to your point, Dr. Miller, is the patients and their families. We think that they must be educated, that one the debridement occurs and the directions are given, that they also have the education. And we plan to have available for them print materials in different languages, videos, and this is for both the patients and the families, 800-numbers so they can call with questions as it relates to their wound care and their treatment and the use of Regranex.

And importantly, we want to do education on recurrence, because that clearly was identified today as an area of concern. We think the more that we can put into education and raise that standard, the better the results will be seen with Regranex out in the marketplace.

MR. C. MILLER: That's the first time I've heard prevention.

MR. JOHNSON: Well, we believe that's going to -- and we know that over the long term we need to show a cost benefit, and we think education will be part of that effort.

MR. McGUIRE: Yes, Dr. Wilson?

MR. WILSON: Yes; just a point of clarification. Somebody had mentioned that hemoglobin A1c should be measured, I think, as a co-variant. And I thought that it was, and I just wanted a clarification of that.

MS. COELLN: Yes, it was, and I believe Dr. Smiell can address that further.

MS. SMIELL: Yes, we did require that people have their glucose under good control to enter these trials, and hemoglobin A1c's were generally under 9.9. We also checked them at end point, and found that they either went down or didn't change very much.

MR. McGUIRE: Dr. Stromberg, let me ask you a question. The -- first, let me point out that time is linear, and we're sliding down it.

And I would like to go on to the second part of question 1, if you have enough information on the first part of the question. The second -- we have five questions to address.

MR. HARKLESS: Could I make one quick comment?

MR. McGUIRE: Yes, just quick as can be.

MR. HARKLESS: Quick as can be. The question was which are the most critical co-variants mentioned, the most critical in the healing of neuropathic ulcers. Clinically, I believe it's really the weight-bearing, as off-loading the pressure, to me. I recognize that there are many co-variants, but to me, that's probably the most critical aspect, I believe, in healing an ulcer, from twenty years of experience.

MR. McGUIRE: Okay. You have -- you're going to get a lot of agreement there.

Okay, let's go to the second part of the question:

"Despite measures to minimize variability, a similar degree of inconsistency might be seen in trials of relatively small size. To overcome noise due to chance, the individual trials should be of sufficient size to detect a statistically significant difference between the becaplermin and control arms.

"Question: Does the Committee agree

that this degree of variability is to be expected for studies of the size presented here today? Does the Committee agree that fewer large trials are preferable to several small trials that have a more homogeneous diabetic population at entry?"

There is a little bit of -- the last -- the second sentence in that sentence, does not state the specificity or the stratification of the large trials. It implies that the large trials will not be quite as homogeneous as the -- as the small trials. I don't know if that was the intention.

MR. STROMBERG: That is the intention.

MR. McGUIRE: Okay. Well, you did sneak it in there, right. Okay.

Can we have some response to that?

MR. WILSON: Can you clarify that last point you just made? That was --

MR. McGUIRE: The notion is that the large trial would not be as homogeneous as the small targeted trials. Is that right, Kurt? Right.

Yes, Dr. Margolis?

MR. MARGOLIS: Isn't this really getting at the issue of efficacy versus effectiveness? And are your trials never going to really be large enough to give you indications of

true population effectiveness, which is true of all drug applications and all drugs that ultimately get approved by the FDA?

I guess I don't quite understand the point of this, because this is going to be a problem no matter how large the trial is. It's just never going to be large enough to reflect the full population. And if the point of the FDA, which it seems is -- in most other studies is actually efficacy and not effectiveness, then why is this becoming an issue in wound healing when it's not in the rest of the world?

MS. WEISS: You're right that the FDA is to -- is charged with determining from the available data whether products are safe and effective. And the issue of effectiveness, of course, is somewhat of a different issue. And whenever you look at a trial, you're extracting or taking a population from the larger community that has the disease. And to some extent, one has to determine how much you can extrapolate or generalize results from that trial to the larger population.

And the question -- and this isn't necessarily unique to what we have here with this particular disease setting, is the idea, though,

that -- and we did some calculations looking at the inherent variability that you see, and we wanted to try to reproduce some of the significant results. One would have to do a trial of about -- a sample size of about 800 or so, 400 per arm, which is quite a large trial, if you really wanted to really ensure that you were going to reproduce the significance that you've seen in some of the other trials, so -- which we're not really asking the Committee about.

I guess more the question is the idea that in larger trials, some of the inherent differences will be -- will not be an issue, just because of the larger sample size, so you don't have to worry so much about some of these slight imbalances in baseline, because of sample size.

MR. MARGOLIS: But you're talking about issues of power, which has to do with the initial trial design, and not necessarily issues of effectiveness. I mean, it -- although it doesn't appear to be true in this case because they did very nice power calculations which I assume the FDA agreed with. If the -- if the effect is so small and the variability is so large, and you are going to need a large trial to show an effect, an efficacious difference -- so again, I don't quite

understand the point. If the normal part of the trial design is that you want a power at .8 and not .65, which is one of the issues that's referred to in one of these documents, then it's not really -- it's not really reflected in this question, because of course you're going to need a large trial.

MR. McGUIRE: There's another -- there's another issue here which I'm not sure I have quite straight, but in Trial F the 30 microgram concentration worked, and clearly it was not effective, or there was no difference between that and vehicle in K. And that doesn't appear to be due to size. The only thing I've heard directed toward that difference was the skill or experience of the -- of the physicians taking care of the patients, or at least I think that -- I believe that's what Dr. Steed said this morning.

MS. COELLN: And infection.

MR. McGUIRE: Infection.

MS. COELLN: And the level of infection in the -- or a lack of -- the level of infection control in the active arm.

MR. McGUIRE: Dr. Wilson?

MR. WILSON: Clinical trials, of

course, are designed to detect treatment efficacy, and not effectiveness *per se*. And there's always a tradeoff, I guess, in terms of how inclusive you become to be more generalizable.

But I think it's probably fair to say that in this day and age it's really not considered good science to perform clinical trials in predominantly white male populations, particularly in a disease like diabetes, which is highly prevalent among black and Hispanic populations. And it could probably be argued that the complications of diabetes has probably even a disproportionate effect in minority populations. And I do not believe that sufficient attention was placed on the representation of minorities and women in this trial.

MR. McGUIRE: That's not the first time that criticism has been heard in these rooms. And the Agency has been rather responsive to that, and I don't know why this population was so skewed. No data?

MS. COELLN: We do have some data on the separation between whites and non-whites, if you'd like to see that. Dr. Smiell?

MS. SMIELL: Well, we did have a

majority of white patients in this trial. There were about -- I believe it was 12 to 13 percent that were black and another smaller percentage which make up "other." And as you can see, the activity of the drug in the non-white versus the white population is similar, again in the smaller ulcer ranges. In the large ulcer sizes, it is again variable, like in the white population. But those numbers are so small in the larger ulcer ranges, that you can't make anything of that.

MR. McGUIRE: Well, I think that's Dr. Wilson's point.

You had a follow-up?

MR. C. MILLER: Yes, I did, on the question. Right before the question, you explained that's how a trial with 500 subjects has always 65 percent power and if you take a 10 percent difference -- now, I'd like to just look at that a little bit.

You're looking at a treatment that you anticipate is going to be effective in about 30 percent of the population. And if I look at 10 percent of that, that's a 3 percent difference between the vehicle and the treatment product. It looks to me like that's not a very ambitious goal,

in terms of your design. I would have thought that you would be looking at, you know, a 10 percent, and not of the level -- but maybe jumping from 30 to 50 percent, which is what you in fact did later, I observe, up to that ending.

So this estimate of the sample size is grossly overestimated in your operating thoughts. Right now it seems to me like we have information that would say some of those treated groups add up to 50 percent. And so maybe that *a priori* estimation process may be erroneous. But we don't know until we find out how the co-variants affected that treatment outcome. Pardon me.

MR. McGUIRE: Would anyone from the sponsor -- anyone from the sponsor want to say anything? And then, Phil, we'll go on to you.

MS. COELLN: I'm not sure that we're -- I'm not sure that we're clear on your question, Dr. Miller.

MR. C. MILLER: Well, it seemed to me like the FDA was concerned about the sample size, and they wanted to know "Should we do a number of smaller, more homogeneous groups, or do we want to do a large, heterogeneous and allow a more diverse population into the study?"

It appears to me that if we are perhaps more ambitious about the difference that we hope to show, that's going to dictate -- a smaller group is effective in this kind of study. And it also suggests that you do want, regardless of the size, to use co-variant type analyses and adjustment procedures. So I don't think we're going to have to go up to 800 observations to be able to show differences in fairly homogeneous groups.

MS. COELLN: I think Dr. Perry has some comments.

MS. PERRY: I can just say that those are sample size requirements that the FDA has mentioned, and we really have no comment on those.

MR. C. MILLER: I see.

MS. PERRY: From our own point of view, our studies were appropriately powered.

MR. McGUIRE: Dr. Lavin?

MR. LAVIN: Let's see, a couple of points here. First off, I count the numbers of subjects from the FDA Table 1 as being well over 800. So they've already done the 800, by my calculations, you know.

Secondly, I think the -- you know, I didn't author this paragraph in the "Detectable

Difference," but I'm sure that the 500, you know, subjects, is to detect a difference from 30 percent to 40 percent. Because that's what the 65 percent power us. That's what, you know, they're looking at here.

So you know, my general sense is that if you're going to do a trial, you know, and you're really going to want to optimize sample size, you should probably pick a trial that looks at the standard care, and ulcer size between 2 and 10 centimeters squared. That's the way to go if you're going to try to do a trial that's the easiest to do, that doesn't require a large sample size. But I think the sponsor here has really probably taken the most difficult road by looking at all comers, you know -- you know, in the same studies, across all four of the same types of populations. And I think that's probably more difficult, so they've really, I think, gone the extra mile here.

MR. McGUIRE: Yes, Dr. Thomas?

MR. THOMAS: To answer the question, you know, to the FDA, I think that the sample sizes in these studies were quite good. In fact, some of the numbers are higher than we'd see in a lot of wound study cases. It's hard to recruit these

patients. And I would favor doing what the sponsor did, and that's using numbers about like they had in order to look at this and get some answers.

Now, if there were a 50 percent difference in treatment effect, that wouldn't be an issue. It's the 10 percent treatment effect difference that's an issue, that requires a larger sample size in order to be sure that it's not variable, which is another question that we're addressing.

So the sample sizes, I think, are fine. And I'd much rather see you guys do small -- smaller studies, because a study of 800 wounds would be just mind-boggling. It just would be -- it would take the next century, even with multi-sites. When you get multi-sites, you get a lot of data in there. And so I feel sort of -- sort of strongly to the effect that we should look at populations like this and determine our clinical questions.

And again, if you're talking about a 20 to 40 percent treatment effect, it's not an issue. If you're talking 10 percent, then yeah, we may have to replicate this. But I would not -- I would not want to see us do size -- sample sizes to try and detect a sample from 30 to 40 percent. I

think that would be impossible.

MR. McGUIRE: I think that's a good summary statement for this question. And I don't know if it will take another century or just into the next century, but it's going to take awhile, yeah.

Let's go -- that was just the warmup question. I have the feeling that the Agency put that, put that question, Question 1, which was a very long and complex question, up there to have us work on all these different issues. And now we get down to really the crucial issue, and it's the one that we've all been talking about. And Dr. Thomas really summarized it, which is the extent of benefit from becaplermin treatment.

"Despite the variable clinical results, there is some consistency of treatment effect in all studies. For example, the percentage of complete ulcer closure in the becaplermin groups is higher than in the placebo, control, or standard care group.

"In the combined analyses, the absolute percentage of subjects who benefited by the use of becaplermin was observed to be 10 percent compared to placebo, and 15 percent compared to

standard care: 43 percent incidence in the 100 microgram per gram becaplermin, 33 percent in the placebo, 28 percent in standard care.

"However, given that in all arms about 35 percent of healed ulcers recurred within three months, treatment with becaplermin resulted in only about 7 to 10 percent of subjects experiencing a durable effect or a durable benefit over placebo or standard care, respectively.

"Question: Is an approximately 10 percent absolute difference in durable complete closure, 30 percent relative, of clinical interest?"

Dr. Lipsky.

MR. LIPSKY: I have some concerns about the issue of the durable effect.

MR. McGUIRE: You're not going to give a yes or no answer?

MR. LIPSKY: Well, if you'd like me to address it in that order. I was going to come at it another way, but --

MR. McGUIRE: No, we can -- we can work around it, but we eventually --

MR. LIPSKY: I could start with a yes, and say that I think that --

MR. McGUIRE: Okay.

MR. LIPSKY: Even if it were only 10 percent, given the seriousness of these lesions, the prevalence of the lesions, the lack of other forms of therapy for these lesions, and the fact that not only do we apparently close -- completely close the lesions more often with this treatment, but do it faster, my answer would be, yes, I'd like to have this available to me in my own clinic.

I do want to come back and address another issue, which has to do with the durability. My understanding of the reason for looking at the durability -- that is, the recurrence rate in this particular treatment -- is to say, is the effectiveness of the way the body heals the lesion different with this product? Do we -- do we close the wound, but with skin that's not as tough as normal skin, if you will? And the answer to that appears to be no, that this product heals wounds in a way that's similar to the way the body would naturally without the product.

The reasons for recurrence have nothing to do with what you do when you treat the lesion. It has to do with what you don't do, which is to prevent the further lesion with off-loading, proper shoes, education, and so on.

So I think to hold the company accountable for -- or the product accountable for the long-term effect is inappropriate.

MR. McGUIRE: Well, I haven't heard that yet. I mean, I haven't heard anyone blame the product or blame the sponsor because these recur. It would have been a wonderful additional bonus if there had been an increase in the durable benefits, but the -- I agree with you entirely.

MR. LIPSKY: But when you reduce the benefit of the product by the fact that because there are recurrences in the future, you take what might a 10 to 15 percent benefit and reduce it to 7 to 10 percent benefit, that doesn't make sense to me. The question is, did the product do what it was supposed to do? And the answer is yes.

If the patient then has a heart attack or another unrelated event, we wouldn't hold the product accountable for that. I don't think we should hold the product accountable for the fact that the patient recurs with an ulcer, because we haven't corrected other underlying problems, either.

MR. McGUIRE: Okay. Other comments?

MR. C. MILLER: Well, I have one observation, and that is, Western society seems to

have the prevalent view that one cure is worth it. And I used to make a point, if it's a 10 percent or 7 percent cure rate, it's worth it. I have kind of a demonstration of that, "Is that one percent worth it?" Well, I'm in a group of spinal cord injury people that is far less than one percent, and I think all those developments are extremely important. And so when I look at something like this, until our society decides that we're going to a cost effectiveness decision-making process for all medical care, I think we ought to stay with our basic Western philosophy that people are worth it, whatever that percent is.

MR. ROSENBERG: The question --

MR. McGUIRE: Okay, Dr. Rosenberg.

MR. ROSENBERG: The precise question is if it will make a clinical difference.

MR. McGUIRE: Correct.

MR. ROSENBERG: An imperfect analogy: I think, you know, would a $300 racquet make a difference for some players versus high-level players that they compete with? And the answer --

MR. McGUIRE: Getting personal.

MR. ROSENBERG: -- is probably yes. If society were to -- I mean, a lot of us know what

we really need are lessons. If society were to send everybody who plays tennis a $300 racquet, how much would the overall quality of the game improve? I would guess not much, not so you could tell it by going out and watching the games.

I mean, we're still dealing with investigators. And these results are all over the map. The variability and heterogeneity of physicians is -- far exceeds that of patients in these studies.

MR. McGUIRE: Actually, I know who you were addressing with regard to the tennis racquet, and --

(Laughter.)

But the issue -- the issue is the 10 percent absolute difference in the treatment group. Is that significant? Is it real?

You know, the other part of that question, and the one that we -- that we do have to give a numerical vote on, is "Has becaplermin been demonstrated to be effective in the treatment of neuropathic diabetic ulcers?" And that's really the point that we've been -- that we've been concentrating on all day, so let's have some -- let's have some discussion on that.

"Has becaplermin been demonstrated to be effective in the treatment of neuropathic diabetic ulcers?"

MR. C. MILLER: At what dose?

MR. McGUIRE: Well, the dose that's being proposed is 100 microgram per gram. I think 30 microgram is off the table, isn't it? Yeah.

MR. MUSTOE: I'll speak. I think, given the enormous variability of wound healing in even the animal situation, I think the overall consistency -- I believe they've proved their point.

MR. McGUIRE: Dr. Hashimoto?

MR. HASHIMOTO: Considering that the number of diabetic ulcers is 2.4 million, a large number of patients out there. And I think -- I don't know how expensive this medicine is, but there's certainly many patients -- even 10 percent, if they definitely improve on this one, I would say this should be available.

MR. McGUIRE: Further comments?

We're not pricing the drug today, luckily.

(Laughter.)

MR. HASHIMOTO: I'd say there should be more a specific label, what type of ulcer.

MR. McGUIRE: Exactly.

MR. HASHIMOTO: What type of area, what location.

MR. McGUIRE: Well, I think that's what we've been hearing from the Committee over and over today. And the Agency has heard us, and certainly the sponsors have heard the Committee.

Dr. Thomas, did you want to comment?

MR. THOMAS: Well, just to take a slightly contrary view, and that is, the clinical trials are showing a 10 percent benefit, and under the best of circumstances, and with a lot of the hard ulcers excluded. And I think in the practice situation, that 10 percent is likely to be less than that. So a clinical benefit of 10 percent in the studies, given the variability among the studies, is going to reduce under general use, would be my guess.

Now, I don't know what number you stop at in terms of whether that's important or not. It may well be important. But what we're talking about is a fairly small treatment benefit that is likely to lessen under general use.

MR. McGUIRE: Well, I think we've heard that the more skilled the provider, the better

the results.

MR. THOMAS: Right.

MR. McGUIRE: And --

MR. THOMAS: This is the best.

MR. McGUIRE: So I think you would not want to get the product, and not a very good doctor. You'd want to -- you would want to get someone who is experienced in dealing with ulcers.

MR. THOMAS: And I think that's a plead-in for very strict labeling.

MR. McGUIRE: I agree. I agree.

Yes, Dr. Wilson?

MR. WILSON: I think clinical trials rarely, if ever, prove anything with respect to effectiveness. On the other hand, I think that the consistency of the results with these particulars trials have -- leads one to think that this is very suggestive that there is a benefit here.

And in terms of effectiveness, there's other factors involved. And I think the educational program and everything else that's going to go along with the distribution of this drug makes me think that not only the effectiveness of the drug, but the -- all the ancillary support that's going to go along with it, would lead me to think

that the distribution of this drug would be effective for a select group of diabetic patients.

MR. McGUIRE: Phil, do you have any comments?

MR. LAVIN: No.

MR. McGUIRE: All right. If anyone would like to comment on efficacy, I'd like to bring this to a vote fairly -- fairly quickly. Someone has a comment?

How many of the Committee feel that becaplermin has been demonstrated to be effective in the treatment of neuropathic diabetic ulcers?

All those yes, raise your hand -- high enough so Tracy can see it. Come on.

MR. ROSENBERG: What are we voting, yes or no?

MR. McGUIRE: This is yes, Bill.

(Members voted.)

Contrary-minded?

(Members voted.)

MR. F. MILLER: May I ask a question?

MR. McGUIRE: Yes.

MR. F. MILLER: May I ask a question of the sponsor?

To get back to the question that I

had asked previously, did the -- were there metatarsal head and heel lesions which did heal? That's the first question.

And the second question is, when Dave showed us the slide of the various groups this morning, and there was variability in the response, in those centers where they had better results, was the off-loading better? Was there better compliance with the off-loading in those particular centers?

MS. SMIELL: The answer is yes, there are metatarsal head and heel ulcers that healed.

MR. F. MILLER: And they were ulcers that had not healed by good other care and --

MS. SMIELL: Yes. The description for the entry criteria, these had to be non-healing ulcers of at least eight weeks in duration, with what was called -- I'm trying to think of the exact word, but we did describe that these had to have an attempt at wound -- good wound care prior to entry. I still don't have specific numbers for you on met-heads.

As far as non-weight-bearing, I don't have it split out by the different centers, but what we did look at were people that were described as being compliant with non-weight-bearing, versus

non-compliant. And the compliant ulcers did have the significant healing separations you saw in the overall results, and those that were non-compliant didn't have those kind of separations.

MR. F. MILLER: How was compliance determined?

MS. SMIELL: It was asked at each visit of the investigator on whether or not the patient was compliant with the non-weight-bearing regimen that was prescribed.

MR. McGUIRE: Fred --

MR. F. MILLER: Yes?

MR. McGUIRE: You raised your hand, and I counted you as a no. Did your hand go up as a question or as a no?

MR. F. MILLER: It went in as a no.

MR. McGUIRE: It went in as a no. Okay. Let me do this -- Tracy and I managed to miss the no vote. How many noes are there?

(Members voted.)

One, two, three, four -- okay. Thanks very much. That's very reassuring I can still count to four; that's good.

Question 3, patients most likely to benefit from becaplermin standard care. And we need

to vote on this also:

"It is necessary to optimize standard care and concomitant therapy in wound healing to compare the benefit derived by becaplermin treatment. Among factors in standard care, there is consensus that non-weight-bearing is essential. Contact casts were not allowed, because this modality is not compatible with daily application of becaplermin. However, for diabetic ulcers that are located over the heel or metatarsal head, total contact casting is considered by many to be the treatment of choice for pressure relief for this class of ulcers.

"Question: Please describe whether the standard of care in these trials was appropriate to allow determination that becaplermin contributed significantly to the healing of neuropathic ulcers. Please discuss your experience with the use of contact casting. If approved, is becaplermin appropriate for treatment of all neuropathic ulcers, irrespective of location?"

Who would like to open that?

MR. HARKLESS: Basically, we use total contact casting -- this is Harkless.

MR. McGUIRE: Go ahead.

MR. HARKLESS: -- routinely for the treatment of neuropathic ulcers. And if you look at the data in the literature by -- about four studies, the average time was about thirty-eight days for the healing of a neuropathic ulcer. So I think that's fits what Dr. Miller's talk clearly alluded to earlier this morning. By about five or six they should heal with appropriate off-loading.

But the question really is the flexibility and the limited joint mobility, which we really haven't talked about, which I think is so important. And if you look at the etiopathogenesis of an intrinsic ulcer, limited joint mobility plays a significant role in that. So I think neuropathic ulcers, really, with total contact cast --

And I guess I would ask the sponsor, did they stratify that out? And I think, from what I heard, that they didn't.

MR. McGUIRE: But your standard of care would be non-weight-bearing and debridement?

MR. HARKLESS: Yeah. I would say the standard of care at each institution is determined by rigidity of deformity and if it's flexible or rigid. If I had an ulcer on my toe and I had a rigid -- semi-rigid to rigid deformity, it was clean

and it was clearly not infected, similar to the one he showed, I would operate on it. I would fix the deformity and then off-load it, and it would heal. And most of the time, once I relieve the deformity, it will heal in about a week or ten days after I do that. I would say that's probably the standard of care for the average aggressive clinician who understands the biomechanical -- biomechanical and surgical etiology of the problem --

MR. McGUIRE: But as --

MR. HARKLESS: -- and the vascular supply, as well.

MR. McGUIRE: As Fred Miller pointed out this morning, the standard of care is not necessarily something that all of us can provide.

MR. HARKLESS: I understand.

MR. McGUIRE: I would never attempt to put on a cast. There are a few people at my institution, and all of whom you know -- there are a few people at my institution who could do that. But it's a -- it is a small -- it's a small arc of the population.

MR. HARKLESS: Right. In addition, we published a study recently looking at the various off-loading methodologies, looking at total contact

casting, DH walker, the Darby shoe, New Balance shoe with the various devices, and about seven different modalities we looked at in our prospective study. And we found that the DH walker actually off-loaded similar to the contact cast, which was a -- which was quite interesting. That's also looking at the felt and foam off-loading methodology at the Jocelyn Clinic that the podiatry group up there utilizes.

MR. McGUIRE: Okay. The Agency has, I guess, put this question in really to get our attention. And this question is a -- creates a dilemma. Obviously, you couldn't apply the medication daily if you had on a cast. And so the question is, did you comply with the best in standard therapy? Well, if you consider a no-weight cast the best, then this wasn't the best. But I think everybody knew that going into the study, so it's a --

MR. HARKLESS: I concur with that. And I think that clearly they demonstrated it doesn't improve the healing rates of the ulceration, so I think -- I already voted on that, so I think that's already clear.

MR. McGUIRE: Other comments?

Dr. Mustoe.

MR. MUSTOE: Yeah, I do think if it's -- if it goes to a labeling question, that the analysis still really hasn't been done. It hasn't effectively been broken out, adequately, I think. The -- if you say that weight-bearing that's difficult to off-load is healing a metatarsal, they really should be analyzed and in a different group, and see. If there is no effect in that group, then I'm not sure the labeling should include that group as part of their indication.

MR. McGUIRE: That's fair.

Other -- yes, Dr. Lipsky?

MR. LIPSKY: I think as Dr. Steed mentioned this morning, there are a lot of places that don't have people who can put on contact casts. Even at his clinic, it sounds like only a relatively small percentage of people have a contact cast put on. It sounds, however, that even in the patients who had the kinds of ulcers that would benefit from a contact cast if that was available, they benefited from this product, as best we can tell with the data stratified, as it is, by ulcer location.

So I think we really can't answer the specific question which was asked, which is "What's the relative benefit of contact casts versus

becaplermin for ulcers that could be treated with a contact cast?" I don't think that study is ever going to be done. But I think there's no reason to believe, based on the available data, that the product shouldn't work on the kinds of ulcers that might also benefit perhaps even more from a contact cast, but recognizing how few places have good technicians to do that.

MR. McGUIRE: It's clear that the -- that one therapy excludes the other, and so these are not going to be used conjointly.

Are there other comments? Wilma?

MS. BERGFELD: Well, I haven't said too much this afternoon. But I'm going to concur in what's said about the first and second question. And I think that we're going to be working out the standards of care, perhaps tomorrow. But I think that as this question is actually stated, they neglected to talk about the other pseudocasts, if we could call them that, that the orthopedic surgeons have developed, that take pressure off the foot and the leg, that could be utilized with such a medication. So I would say that pressure -- relieving pressure over a period of time, with the use of this active ingredient, might be very helpful

in some of these patients. And I would prefer to use it in that sense, rather than to say specifically contact casts, because of what's been said, that there's some limitation in the ability to put on such a cast for a number of reasons.

MR. McGUIRE: Okay. Are there any comments over here? Yes?

MR. F. MILLER: I would agree with what Wilma said, you know, that there are other approaches, not just the contact cast. And maybe in the discussion this morning it looked like that was the only way, and there certainly are other methods. And you know, we've tried the Jocelyn method and the various orthoses.

And also, the other point that I would like to make is, with the education, educational arm of this, that if you teach people how to debride, which is really a great idea, at the same time there's going to have to be an arm that deals with off-loading, so that if physicians do use this preparation -- you know, the *sine qua non* in therapy is to avoid pressure, in addition to the debridement. So there's going to be something needed in that regard.

MS. COELLN: That is something that's

in our labeling, as well as will be in part of our education. We will address that.

MR. C. MILLER: Can I just ask a quick question?

MR. McGUIRE: Yes, Dr. Miller.

MR. C. MILLER: It is my concern that, real or imagined -- that a physician in the field might confuse the use of the staging system you're using here with the staging system that's used in pressure sores. Is that of concern?

MR. McGUIRE: Well, it's always a concern. But I don't think -- you know, the discussion has really been directed toward neuropathic ulcers. And you may be asking me whether there's somebody out there that doesn't know the difference between a neuropathic ulcer and a pressure sore, and I guess there is. But at least the intent is not to be treating stasis ulcers, not to be treating ischemic ulcers, not to be treating other kinds of ulcers, but to be treating neuropathic ulcers, which to the best of my knowledge, most diabetic ulcers are. There are some that are not neuropathic, but most are. And I think that's -- I think the sponsor has made that very clear. If somebody out there is going to get

confused about it, I'm sure -- will it be used for the wrong indications? Sure.

MR. ROSENBERG: Could I ask about that, Joe?

MR. McGUIRE: Yes. Dr. Rosenberg.

MR. ROSENBERG: If this helps the tissues, if it motivates the tissues to heal, why does it only work on neuropathic ulcers? Why shouldn't it work on the others?

MR. McGUIRE: I don't know that we've addressed -- I don't know that we've addressed that. Does the sponsor want to wade into that?

(Laughter.)

MS. SMIELL: I think the key point that we're talking about is neuropathic versus ischemic. We didn't test it on ischemic ulcers. We know that oxygen is very important in the healing process, and that's why we excluded those folks.

The etiology of other types of ulcers, especially the venous ulcers, is different, and so that's a different testing program.

MR. McGUIRE: And so the answer is, you don't have data that you can -- with venous stasis ulcers?

MS. SMIELL: We don't have it with

venous, but we do have it with it with pressure ulcer, which shows efficacy of 100 microgram per gram concentrations.

MR. McGUIRE: Okay. Dr. Lipsky.

MR. LIPSKY: We've talked about the difference between the neuropathic and the venous stasis ulcers. I think there's another important distinction to make, which is the diabetic and the non-diabetic. In the wonderful talks we had this morning, one issue that wasn't really addressed was the fact that there appears to be some underlying immunological perturbation that diabetes causes that also affects the susceptibility to infection, the likelihood of developing wounds, and the lack of healing of those wounds.

So to take the data from these studies and transpose them to other types of patients who have, for example, pressure ulcers, but are not diabetic, I think is fraught with all kinds of difficulties.

MR. McGUIRE: Well, let's not do it, then.

(Laughter.)

I think it would take a lot of -- a lot of time to sort that out. And I'm not sure that

everyone would agree with the immunologic problem in diabetics. It's rather surprising to me that one can have an open ulcer for three years and not have a clinical infection.

Let's focus on the question:

"Please discuss whether the standard of care in these trials was appropriate to allow determination that becaplermin contributed significantly to the healing of neuropathic ulcers."

And I think we can just say yes or no on that one, agreeing -- agreeing up front that there are different standards of care. And the standard of care which permitted this study to be carried out precluded using a cast, full casting.

Does anyone want to ask a question before the vote?

I am reminded that the question mark occurs after "location," not after casting, so "If approved, is becaplermin appropriate for treatment of all neuropathic ulcers, irrespective of location?"

That's a little more complex. Who would like to comment on that?

MR. HARKLESS: I mean, I would have a concern about the location, as related to the

interdigital aspect versus the top of the toes, in terms of the lesion. Because if you look at a toe, there's nothing there but -- once you go through the skin, you're down to the capsule of the joint. So you're looking at a whole different etiology and how it spreads, versus the plane of the foot, where you tend to have more subcutaneous tissue. You debride the callus, you'll have granulation tissue. But once you break the skin on the side of a toe interdigitally or in the web, to me, it's a deep ulcer at that point. And in the classification system the staging would change, potentially.

MR. McGUIRE: Dr. Lipsky?

MR. LIPSKY: Just one quick point. If you're going to vote on this question, I think what's left out of the question is the word "diabetes" and the word "foot." So as it's stated, you could use it on any neuropathic ulcer in any kind of patient.

MR. McGUIRE: Agency accepts that?

MS. WEISS: Yes. Thank you very much.

MR. McGUIRE: Okay. Is there other discussion?

MR. WILSON: Question. Are we going

to be voting on two questions or one? It seems like there's two questions here.

MR. McGUIRE: It's one. It's one question. It's a "Were it to be approved," okay? Just deal with that. Then, "Is becaplermin appropriate for treatment of all neuropathic ulcers" -- "diabetic neuropathic ulcers, irrespective of location on the foot?" And so the -- we're not voting on the first one; that's "Were it to be approved."

Mrs. Cohen?

MS. COHEN: I have trouble with the word "significantly"; that's a very strong word.

MR. McGUIRE: Okay, that's -- okay, I understand. But that's not in the -- that's not in the question. The question is that -- the question really begins with "If approved, is becaplermin appropriate for treatment of all diabetic neuropathic ulcers, irrespective of location on the feet?" I agree it's a little confusing, and I missed the point -- I missed the point myself.

Are we ready to vote on this?

Dr. Mustoe?

MR. MUSTOE: I just would restate my previous concern that I don't think they've analyzed

the data. They haven't broken it down by location, other than just to say that most, 70 percent, are the forefoot, but did not break down the -- at least in terms of their percent healing, or maybe I missed it, between toe and metatarsal head. There were a very small number of heel ulcers, so that the largest number in the study and the ones who did the best, which weighted the results, were on the toe. So I don't know that we have enough information for me to be able to say that it's -- that it's efficacious in all locations.

MR. McGUIRE: Okay. Well, I think that's an important question. Would the sponsor like to respond to that?

MS. COELLN: What?

MR. McGUIRE: The question is, do you have -- do you have enough data to carry this question? Do you have enough -- do you have enough data on different parts of the foot to carry this question?

MR. HARKLESS: A quick comment while she's coming?

MR. McGUIRE: Sure.

MR. HARKLESS: I think the staging would play a role as it relates to the location,

because if it is a superficial ulcer, and which all of these particular studies demonstrated, then even if it was on the toes, it could fall in that category. Because if it's just very superficial, I make the comment that it could be down in the tendon and bone. But I have seen interdigital ulcers that may not be down to the tendon or bone, but if it does probe to tendon or bone, then it would change. I would be concerned about the location.

MS. SMIELL: We do have the potential to run that data, but we do not have that data today on toe versus metatarsal head, versus heel. All we have are forefoot, mid-, and hindfoot combined, and leg, which includes the ankle.

MR. McGUIRE: Well, Dr. Mustoe, unless -- unless someone pushes or pulls, I think we can leave that question unanswered, since we don't have the data. Okay.

And now we're in Question 3(b), ulcer staging:

"Clinical trials of becaplermin were performed in diabetic patients with Stage III, defined as full-thickness tissue loss extending through dermis to involve subcutaneous tissue, or Stage IV, neuropathic ulcers.

"The sponsor has not examined becaplermin in trials of more superficial Stage II ulcers. The phrase 'full-thickness through epidermis and dermis' has been proposed by the sponsor to describe ulcers appropriate for treatment with becaplermin.

"Likewise, becaplermin has not been examined in diabetic patients with ulcers due to vascular impairment. All becaplermin-treated patients had a TCPO2 of greater than 30 millimeters of mercury.

"Question: If approved, should the sponsor's definition be used, or should labeling specifically state that becaplermin is intended for treatment of neuropathic ulcers that extend at least through subcutaneous tissue, Stage III, and in which there is an adequate blood supply."

Discussion? Yes, Dr. Margolis?

MR. MARGOLIS: This is a question I've been wondering about for a while. How does the sponsor propose that the family practitioners, who have been mentioned a few times as being those who may be using this -- how will they do TCPO2's? Or has the technology become very available in the last couple of weeks?

MR. McGUIRE: They'll probably do ABIs.

MR. MARGOLIS: But is there a tight correlation from their study between ABI and TCPO2?

MR. McGUIRE: Let's get some help from the sponsor.

MS. SMIELL: What we've proposed now is that a noninvasive measure of the adequacy of perfusion be done, whether that's ABI, laser Doppler, PVRs, whatever is chosen.

MR. MARGOLIS: But your analyses were all based on TCPO2's, right?

MS. SMIELL: Yes, they were.

MR. MARGOLIS: Have you shown that there's a tight correlation between laser Doppler, TCPO2, and ABI?

MS. SMIELL: In this population, as you know, ABIs may be difficult to interpret because of calcified vessels.

MR. MARGOLIS: So, then, you can't use that, correct?

MS. SMIELL: Correct.

MR. MARGOLIS: So then we're down to TCPO2's.

MS. SMIELL: Palpable pulse. And

people with palpable pulses, the majority of those patients have a TCPO2 of at least 30. And I think Dr. Steed is probably the person to ask specifically about noninvasive vascular testing that would be appropriate in this situation.

MR. McGUIRE: Well, but I think -- I think the question that Dr. Margolis has brought up is whether this type of staging is going to be practical. Are physicians going to be able to do a TCPO2, since the ABI is not going to -- may not be that informative, unless you have correlations. And I think you do not have correlations, for the reasons stated.

MS. SMIELL: It's not for the staging, it's to determine the adequacy of perfusion and the difference between ischemic and neuropathic.

MR. MARZELLA: Can I make a comment?

MR. McGUIRE: Yes, Dr. Marzella, go ahead.

MR. MARZELLA: You were asking that the -- we're not asking for a specific definition of adequate blood supply. Is --

MR. McGUIRE: Dr. Marzella, I can't hear you.

MR. MARZELLA: We're not asking for a

specific definition of what constitutes an adequate blood supply. I think this morning there was a discussion of a lot of different way by which clinically one can determine adequate -- adequacy of blood flow. So the intent would not be to require that necessarily TCPO2 measurements be done.

MR. MARGOLIS: But the data is all based on TCPO2, correct?

MR. McGUIRE: Yeah; the question is, how is that going to be done? Dr. Thomas?

MR. THOMAS: I'll answer that, and then I'll pose another question.

I think what they're trying to say is that there needs --

MR. McGUIRE: I think your microphone is dead.

MR. THOMAS: It'll come up in a second; there's kind of a lag, like the Mars lander.

(Laughter.)

I think there's definitely got to be enough labeling data to be sure that this is not used in ischemic, and the methodology is going to be, they basically prove that it's not -- or be assured that it's not going to be ischemic. And it's going to be open as to how people do that. And

you and I know that they're not going to do it right, and they're not going to use oxygen and all that.

So I think it's just -- it has to be really stressed that this is -- this is not for, you know, ischemic, that needs to be treated differently, and that because of the educational problems that you guys have already talked about, that has really got to be educational in the package label.

Now, the other issue is, then, in terms of the staging process. Which staging system are we using? Are we using OBRA? Are we using Wagner's? Or --

MR. McGUIRE: Dr. Smiell?

MS. SMIELL: We would prefer not to use a staging system in the label. Because as Dr. Steed mentioned earlier, and perhaps he can address it again, because there are so many different types of staging systems, it becomes very confusing.

MR. THOMAS: Well --

MS. SMIELL: So we would like to use some sort of description of the ulcer.

MR. THOMAS: Well, I think that there are two components to that. One is, I'm just

curious as to which -- when you talk "stage" here for these studies, what are you talking?

MS. COELLN: Jan, what was the name of the staging system that we used in our clinical trials? And actually, we have a diagram of what that --

MR. THOMAS: Well, I don't need to -- I just --

MS. SMIELL: Okay. Stage I is --

MR. THOMAS: Did you have four stages?

MS. SMIELL: Four stages.

MR. THOMAS: Five stages?

MS. SMIELL: Four stages.

MR. THOMAS: Four stages. 8 CPR?

MS. SMIELL: With I and II being partial and III and IV being full thickness.

MR. THOMAS: 8 CPR instead of the 5?

MS. SMIELL: Yes.

MR. THOMAS: So when you -- when you do that, or when you talk about these stages, if you're going to talk in stages, you're going to have to have to define it in terms of which staging system you're using, or otherwise you're going to get confusing problems of people who are using

Wagner's.

Then the other issue is that if you're going to put something the thickness of a dime into a wound, it's got to have enough depth for you to be able to do that, which by definition is going to be a III or IV. So I assume that you're not talking about trying to use this on a I or a II.

MS. SMIELL: No, that's correct, all our studies were done on III and IV, based on this.

MR. THOMAS: Okay.

Well, for purposes of labeling, that's going to be really hard. We've been trying to do this for probably about three or four years, 8 CPR guidelines, and it's still people do not understand it. So I think you're going to have to be careful to explain that.

MS. SMIELL: Okay.

MR. McGUIRE: So you would like to see an anatomic definition of the staging?

MR. THOMAS: I think you're going to have to tell people what to look for. But you also are going to have to make it plain that if you're going to put something the thickness of a dime in a wound, it has to be the depth of a dime.

MR. McGUIRE: Okay.

MS. SMIELL: Yes.

MR. McGUIRE: Now, Dr. Margolis, I have a question for you. Would you be more comfortable with the question if, instead of ending with "in which there was" -- "in which there is an adequate blood supply," it was stated that "the patient had a TCPO2 greater than 30 millimeters of mercury"?

MR. MARGOLIS: I'm not really sure whether I'd be more comfortable with it, to be honest. My greatest concern is part of the concern that everybody's had about something that isn't -- that has 10 percent efficacy, that's now going to go out to the real world and may or may not be generalizable.

And there were fairly specific inclusion and exclusion criteria used in each study. And if the TCPO2 is important for adequate blood flow, which lots of studies have shown that it is, if people begin to violate that, then right from the bat you may end up with a product that doesn't look effective in the community, which really is effective if it was being used correctly. I just hate to see something fail, especially this being the first of what will, hopefully, be several

products -- fail and sort of get a bad reputation for the whole group of products, when it's just not being used correctly.

MS. SMIELL: We agree with that.

MR. McGUIRE: Okay. Dr. Steed has a comment.

MR. STEED: Yes. When we designed the first trial, we wanted some objective measurement to assure us and to assure other people reviewing the data that the wounds were not ischemic. And we chose the TCPO2 of greater than 30, since the literature would suggest that's an adequate blood supply to heal. We by no means mean that every patient should have a TCPO2 over 30 to heal a wound.

I a couple of years ago went back and looked at 200 consecutive diabetic ulcer patients that I saw myself in the clinic, and I had a medical student go back and read every clinic note, and I had a note on every patient. And I could palpate a pulse in 68 percent of those 200 patients that came through the door, so about two thirds -- and I believe it was palpable because I examined them all myself and noted it in the -- in the patient's chart.

So I would suggest if you have a palpable pulse, that you have an adequate blood supply. And I believe -- I mean, physicians -- every physician here who sees patients with diabetic ulcer assesses blood supply. You don't need a TCPO2 to do that. But you should say that they have an adequate blood supply by whatever means you use, and certainly if you have a palpable pulse, most would not order any noninvasive studies except in an unusual circumstance.

MR. McGUIRE: But I still think there will be some discomfort in using criteria other than were used in the clinical trials. And the criterion you used in the clinical trials was a TCPO2.

MR. STEED: Right. But we wanted some -- we wanted some objective number, so that someone couldn't come back and say, "This one was ischemic." So if they had TCPO2 of 30, whether they had a palpable pulse or not, we still made them have a TCPO2 over 30. It turns out that the average TCPO2 in that trial was 56, and normal is 55 or greater, so they were essentially -- essentially normal blood supply.

I can't remember -- and certainly we have a wide experience in TCPO2, because we do a lot

of clinical trials and we have a unit in our clinic, and we use it fairly liberally. If you have a palpable pulse, you'll have an adequate TCPO2 in almost every case. But I don't think we should restrict physicians in practice to measuring TCPO2, to use this. We should have them be convinced there's an adequate blood supply. And a simple -- if you can palpate a pulse, it will be adequate in most cases.

MS. COELLN: I think if I could add something to this conversation, in the clinical pharmacology section of our proposed labeling, where we describe the clinical trials, we do include the fact that we evaluated the perfusion in these ulcers with the TCPO2, and the requirement was to be greater than or equal to 30 millimeters of mercury.

MR. McGUIRE: Dr. Lipsky?

MR. LIPSKY: If the intent is to exclude patients who have ischemic as opposed to neuropathic ulcers, might a change in wording be that it's appropriate for treatment for ulcers that are predominantly, or at least predominantly neuropathic, so it gets at the point that you're pretty comfortable, as the treating physician, you're treating a neuropathic and not an ischemic

ulcer?

MR. McGUIRE: Yeah, if we ever answer question 3(a), that will be built into 3(a).

(Laughter.)

I mean, 3(a) was restricted to diabetic neuropathic -- I didn't -- I'm not making light of your question, but I mean it's built into that. The only reason that 3(a) was not -- was not answered, is because we haven't -- we do not have a stratification of the data from different locations in the foot. But I think it's every intention that this -- that we're talking about diabetic neuropathic ulcers. I don't care if it's in the answer to 3(a) or 3(b) or wherever.

But the 3 -- 3(b) is talking about something a little bit different, and the "If approved, should the sponsor's definition be used, or should labeling specifically state that becaplermin is intended for treatment of neuropathic ulcers" -- do you want to put "diabetic" in front of "neuropathic" there?

MR. LIPSKY: No, that's not the point I was making.

MR. McGUIRE: I mean, "that extend at least through subcutaneous tissue," we agree that's

important, "and in which there is an adequate blood supply." And then I think there needs to be a little more language there about the adequate blood supply, which is at least palpable pulses.

MS. SMIELL: Can I make one more point on that, for the definition "through the epidermis and dermis and into the subcutaneous," not "through the subcutaneous"? Because that was our definition for Stage III.

MR. McGUIRE: Dr. Bergfeld?

MS. BERGFELD: That was the question I was going to ask.

MR. THOMAS: But "extending down to the subcutaneous tissue" is -- okay, if it goes into the subcutaneous tissue, it's a III.

MS. SMIELL: Yes.

MR. THOMAS: Okay.

MS. SMIELL: That's what we're calling full thickness, not -- we don't require that it be completely through the subcutaneous tissue.

MR. THOMAS: Right.

MS. SMIELL: Yes.

MR. THOMAS: If it does and goes down into muscle, it's a IV.

MS. SMIELL: Right, then it becomes

IV.

MR. McGUIRE: Dr. Wilson?

MR. WILSON: All right, just a point of clarification. My impression was that in the trial there were patients who had a TCPO2 that was greater than 30, who did not have a palpable pulse. And I would not be in favor of your amendment, which would include having a palpable pulse.

MR. McGUIRE: Well, I think it would be the other -- I think it would be the reverse of that that you would be concerned about, if someone had a palpable pulse and did not have an adequate TCPO2.

MR. WILSON: Right.

But my understanding was, and this is not my area -- my understanding was that if you have an adequate pulse, you almost always have a TCPO2 that's greater than 30, but that you can have a TCPO2 over 30 and still not have an adequate pulse. And so I would think that if you had an adequate pulse, that begs the question and that's fine. But there may be people who may not. And if you restrict it to just those people who have a palpable pulse, then you may actually miss some people who may benefit from this treatment, who would have a

TCPO2 over 30. That was my point.

MR. McGUIRE: I guess I was looking at it in a little different way. I didn't want to offer this therapy for someone who would not benefit. Dr. Steed, do you care to comment again on that issue?

DR. STEED: Sorry?

MR. McGUIRE: The question, should you exclude -- should you exclude patients who do not have a palpable pulse?

MR. STEED: Well, I guess if they had a palpable pulse, then it's obvious they have enough -- I mean, I think they have enough blood supply. If they don't then I believe it's up to the clinician. If you believe that they don't have a palpable pulse, most clinicians are probably going to do some type of noninvasive study to be certain they have an adequate blood supply. And they would do that even if they didn't used this product. I think most of us here who have taken care of a diabetic foot ulcer, if they didn't have a palpable pulse, would try to do some vascular laboratory testing to be certain they had adequate blood supply and did not need revascularization.

MR. McGUIRE: Dr. Thomas?

MR. THOMAS: Well, just a comment about palpable pulses. We're going to have to solve the problem of ischemia a different way. Because one of the statistical things, you know, that they do when they teach you the kappa statistic for agreement between observers, is a study of palpable pulses. And there's absolutely no agreement. And I would offer that most people in this country can't find a palpable pulse.

(Laughter.)

So I mean, it really is a problem. I mean, I understand and agree with you that if you feel a good pulse, then that's fine. That, to me, rules out ischemia. But you can't -- that can't be a criterion in the labeling process, because most people have a tremendous difficulty feeling pulses.

MR. McGUIRE: Dr. Simmons-O'Brien.

MS. SIMMONS-O'BRIEN: I agree that labeling for ischemia is going to be different. And one of the things I'm concerned about, hearing the discussion, is the patient who not only is a diabetic and has diabetic foot ulcers, but who also has connective tissue disease, who may in fact have lupus, and may actually have small -- small vessel -- small vessel disease. So I think many oftentimes

when people hear "non-ischemic," they immediately think, "Oh, it's an arterial ulcer." Well, there are more than arteries at stake; there are also small vessels.

And how can we help guide the practitioner to make certain, when they have a patient who has more than diabetes, to know exactly whether they're dealing with a diabetic ulcer or possible an ulcer as related to their connective tissue disease process in the same vicinity?

MR. McGUIRE: Well, that can very easily be put into the language, I think, that --

MS. COELLN: I believe --

MR. McGUIRE: -- other vasculopathies -- other vasculopathies should be considered.

MS. COELLN: I believe Dr. Robson had something that he wanted to add.

MR. McGUIRE: Please.

MR. ROBSON: Yeah, I'm concerned a little bit. Don't you really want, on this ischemia question, to -- in your labeling or in their educational package to say, "If they don't have palpable pulses, they need to be evaluated to see if they have correctable vascular disease before you use this drug"? Because just because it wasn't done

in the clinical trial, all the pre-clinical and the data that Tom Mustoe showed today suggest this might be very good in ischemia, and may be one of the few cytokines that is.

And therefore, I think what you really want to do in your labeling is say, "When you work these people up, however you do it, by TCPO2 or palpable pulse, if you think they're ischemic, that should be ruled out." That should be part of the labeling and part of the educational thing.

But I'm not sure it should be exclusive, because what if you then send in the vascular surgeon, they say they can't be corrected, or the patient refuses to be corrected or refuses an amputation? There is no data that suggests that this agent would not be useful in that patient. And so I think you want to have it more as an educational in the labeling than exclusive.

MR. McGUIRE: Okay. Thank you for your comments. I don't think the Committee is within a mile of suggesting that it be used for indications other than were -- than were examined in the clinical trials. But I think you're correct, in that if there is a question, then the patient should be worked up.

We've just about beat this question to death, I believe. Yes, go ahead.

MR. HARKLESS: There is a subset of patients that can have a palpable pulse, and it's a paradox that they still may not heal. And there is an entity in the literature that's called signal ischemia, and so I'd think that that, in addition to the fact that you can have connective tissue disease -- I think that begs the question as well.

And to me, the question arises, does the patient have the signs and symptoms of vascular disease in the foot and leg? And maybe that should be included in the package -- and also, hopefully, that the average physician would know what the signs and symptoms of vascular disease in the foot and leg would be, in addition to the fact that they may or may not have a palpable and loud pulse. But I don't think you can put all your money on the fact that they may not -- they may have a palpable pulse, and they still may not heal a distal neuro- -- or ischemic ulcer.

And if you think about this slide that Dr. Miller showed this morning, I can give you numerous cases where our patients have had an ulcer at their hallux and phalangeal joint of the first

metatarsal, and it didn't heal after off-loading. And once we obtained an appropriate arteriogram, they had occlusive disease in the medial plantar artery. That was the only thing that was actually shown. They had three-vessel runoff, but they had islands of ischemia that did not heal. And so I think that's important, as well.

MR. McGUIRE: Yeah; thanks for emphasizing that. That was really the point of Dr. Simmons-O'Brien's comments.

Let me read the question again. This is Question 3(b):

"If approved, should the sponsor's definition be used, or should labeling specifically state that becaplermin is intended for treatment of neuropathic ulcers that extend at least into subcutaneous tissue (Stage III) and in which there is an adequate blood supply?"

Remember, this is all "Were this to be approved." Can we have a vote? Who's in favor of this? Let's raise them so that Tracy and I will get the counts right.

(Members voted.)

Thirteen. Okay.

Opposed?

(Members voted.)

Abstain?

(Members voted.)

We have one -- two abstains, two abstentions. Okay.

I propose to go through these questions without taking a break. I think if we take a break, we will lose our momentum, and so let's just -- let's just keep going. Is everybody just too tired to respond to that? I didn't hear anything. Okay.

(Laughter.)

"The appropriate formulation, drug concentration, and administration (drug amount) of becaplermin.

"Selection of drug concentration. The 30 and 100 microgram per gram formulations were effective in some of the trials" -- I think that means "if" -- "but in the K Trial, where both formulations were compared, only the 100 microgram per gram formulation was effective.

"Does the Committee agree that the 100 microgram per gram formulation should be the approved formulation?"

Is there discussion on that?

As you recall, the data with the F Trial or with the F Study looked very promising for 30 microgram per gram, and then in the next trial, the K Trial, that difference -- that difference was lost. And we have speculations why the difference was lost, and we heard Dr. Steed explaining his ideas. And the sponsor wishes to go with the 100 microgram per gram. Would anyone like to discuss the concentration?

No discussion. Let's vote yes or no. I vote yes. Who votes yes?

(Members voted.)

Thirteen. Okay.

No?

(Members voted.)

Abstentions?

(Members voted.)

One, two -- one, two. Okay.

MR. ROSENBERG: I'm just looking forward to seeing some nice, clear, straightforward clinical data on the Rogaine day; I'll just put it that way.

(Laughter.)

MR. McGUIRE: If you can erase that, erase it. Okay; and in that case, that was Dr.

Rosenberg. Okay.

(Laughter.)

"Does the Committee agree" -- okay.

The amount of drug administered. And there was some discussion about whether it should be thin as a dime or it should be administered as length or as weight.

"In Studies F, K, and 001, measured doses were used on an ulcer" -- "based on ulcer area. In Study 002, the dose was not measured and the portion of becaplermin-treated subjects that had complete healing was the lowest of all major trials.

"A comparison of drug usage and clinical outcome in the 002 Trial showed even greater excessive usage, about eightfold more micrograms per square centimeter, on average, than the expected amount. In actual usage, the potential exists for dose application even in greater excess than that which occurred in Study 002.

"Topical agents are not delivered in measured doses. The sponsor believes that the data demonstrate that the concentration, micrograms per gram, and not the amount of gel applied, is associated with the efficacy outcome of becaplermin gel. Consequently, the sponsor has proposed the gel

be applied as a thin continuous layer, thickness of a dime, and does not wish to include instructions for measured dosing in the label."

And now the -- okay. And now the question:

"If becaplermin is approved, should instructions for measuring dosage based on ulcer area, as was used in three of the efficacy trials, be recommended in the label?

"Please discuss the possibility that excessive administration of the drug might diminish efficacy."

And then the second part of that:

"If becaplermin is approved, please discuss whether there should be further post-marketing exploration of drug concentration (amount applied to the ulcer), or other dose-related issues, such as schedule."

As I looked over the early data from the sponsor, it occurred to me that there might be a biphasic response to the drug, and at least in a clinical situation, that too much was not as good as the right amount. I think that that question comes up again.

I don't -- I'm waiting to hear from

people who can advise me on this. I don't -- I don't understand that these are the only issues involved in that 001/002 clinical trial. Are there comments? Tom? Dr. Mustoe?

MR. MUSTOE: Yeah, I've got a couple of points on that.

Number one, from animal studies there really -- although there is some evidence of biphasic dose responses for some growth factors, notably TGF-beta, their 1 and 2 and 3, there is none that I've seen for PDGF on the -- and so I'm not sure that's a major concern.

On the other hand, the company's statement that 100 micrograms -- that it's the concentration that's the important issue, I find their data totally non-compelling on that issue. I don't -- there's no data. I don't think their human data is conclusive on that issue, and there's no data that I'm aware of that say the concentration of the drug is an issue.

And I think right now I would have to say that I think that the dosing is important, and that the -- and that certainly this is one area that, given the drug's expense, I think the patients must be in every way -- labeling must be that more

is not better.

MR. McGUIRE: Is there other discussion?

MR. MUSTOE: Just one more.

MR. McGUIRE: I mean, it is with other products. With other products, one can -- one can adjust the dose to fit the area, and there are algorithms for doing that. You know, a half inch covers an area this by this, an inch covers and area this by this. And applicators have been designed that dispense given amounts, so that's not -- that's technically not very complex.

I think the issue that I'm hung up on here is the concentration versus amount. And I agree with Dr. Mustoe, I don't think -- I don't think that question has been answered, unless it's about to be right now.

Dr. Coelln.

MS. COELLN: What I think we have is some additional information related to the amount applied, and that it's lack of -- yeah, in 002, and how that related to outcome.

What you see here is the micrograms of becaplermin applied per centimeter squared of ulcer area, for the study DBFT-002. And it shows

that the amount of the actual becaplermin applied to the ulcer is comparable for the efficacy outcome.

Jan, do you want to say something?

MS. SMIELL: Actually, we looked at this in several ways. This graph takes into account just the baseline ulcer area. The graph that I showed during my presentation took into account the ulcer area at every visit, and how the micrograms per centimeter squared per ulcer area compared.

And if you put up slide No. 16, I believe 16 will also show percent compliance, again similar to what I showed in my presentation. Number 16; slide 16 in the backups, please.

What this is, again, is the DBFT-002 study. There was concern that perhaps too much drug application affected the efficacy outcomes. That was K. Okay.

DBFT-002, and this is again percent compliance, which took into account what was prescribed over what -- what was used over what was prescribed. Okay? And we went and calculated back to that. Even though they didn't measure in this study, we did our calculations based on what would have happened if they had measured.

Here you see percentage of ulcers

healed on the Y-axis, and this X-axis is the compliance percentage. Here would be the zero to 100 percent compliance. And again, we don't take into account waste. And you see that even up to 1500 percent compliance, for this study you still get efficacy with the becaplermin gel.

MR. McGUIRE: I'm not understanding that slide.

MS. SMIELL: Okay.

MR. McGUIRE: Are you telling me that if you don't use the -- that if you don't use the drug, you get 50 percent healed?

MS. COELLN: No; what it says is that as long as you cover the surface of the ulcer with the gel, that you get efficacy. And the reason we say the concentration is the relationship, because it's the concentration of the gel that meets the wound's surface.

MR. McGUIRE: I guess I didn't get the definition of "compliance."

MS. SMIELL: "Compliance" is the percentage -- is the amount of drug used over the amount of drug that would have been prescribed for that ulcer area, times 100.

MS. COELLN: And the prescribed

amount here is the calculation that was used in the first three studies, so it was based on the length times width measurement at each visit.

MR. C. MILLER: Those people on the right participated, in that they believed that more is better.

MS. SMIELL: Yes, but as you saw in my presentation slide, even when they calculated the dose and had it prescribed in, you know, partial centimeter, centimeter of gel that was to be used, they still had a very wide range of how much they actually put on their ulcer.

MR. ROSENBERG: It looks like those that used 200 to 300, you know, dropped down to placebo levels.

MR. McGUIRE: Okay, let's get things in order.

MS. SMIELL: There's nine patients --

MR. McGUIRE: I have a question over here from Dr. Thomas.

MR. THOMAS: Well, just a comment to say that I think that if the concentration is important, then I would strongly urge you to put some dosing schedules into the labeling. Because in practical terms in the field, people are going to

use big squirts of this stuff, thinking that using more of it is going to be helpful.

So I would think that if we can get by with less in terms of amount, and there's no change in efficacy, which you seem to show, although I'm not convinced, then I would -- I would strongly urge you to put some guideline in there that says it just has to be covered.

MR. McGUIRE: Dr. Lavin, you had a question? Did not have a question.

Dr. Margolis, and then back to Dr. Rosenberg.

MR. MARGOLIS: You need to show data from Study 002 where standard care and agent had the same effect.

MS. SMIELL: Yes, we can show you the other individual studies.

MR. MARGOLIS: But with maybe more --

MS. SMIELL: But they're basically the same, that it's not the amount of gel that's applied, but it's the actual concentration. In this case we've already chosen the .01 percent, the 100 microgram.

MR. McGUIRE: Could you go back, I think to the slide that Dr. Coelln had on, that had

the amounts, the improvement on the ordinate and the amounts across the abscissa? I think it's a slide.

MS. COELLN: 45.

MR. McGUIRE: One slide ago, two slides ago.

MR. ROSENBERG: It's a projection. That's it, no?

MS. SMIELL: This is calculating the actual amount of drug substance.

MR. McGUIRE: No; it's the one before that.

MS. COELLN: Laurie, can you put the slide on, slide 16?

MR. McGUIRE: Yeah; take the overhead off.

Okay, now, I don't see a trend.

MS. SMIELL: That's the point.

MS. COELLN: Yeah, that's why we don't think it needs to be measured, because --

MS. SMIELL: There is no trend. What this says is that as long as you cover the surface of the ulcer with a layer of gel, that you get whatever efficacy you're going to get for that ulcer. And it's not the thickness of the layer or thinness of the layer, it's just the fact that you

have the ulcer surface covered.

It's really the concentration at that surface level of the ulcer that gives the efficacy. No matter how much becaplermin or gel you pile on top of it, it's the activity at the surface layer, based on concentration, that matters.

MR. McGUIRE: Dr. Rosenberg?

MR. ROSENBERG: I just -- again, it looks like -- if the 100 is what you want in terms of microgram or whatever, that 2- to 300 isn't very different when one is using topical products. The one right after the --

MS. SMIELL: Right. There are nine that --

MR. ROSENBERG: No; the next one. The next one. That level of percent healing is no better than you get with standard care or placebo, and that's not very much more than the other. You know, it seems that we picked some bars to consider true and others we are willing to disregard in this study. I don't know how we decide.

MS. SMIELL: Keep in mind that the ends here are very small down here at this range, and you have to wonder if this is underdosing because of missed doses. And it's this group in

here, that have the higher ends, that you need to look at.

MR. ROSENBERG: That isn't --

MR. McGUIRE: Dr. Margolis, did you have a question?

MR. MARGOLIS: No, it's just -- you just said it's no better than placebo, and that was the result of that trial.

MS. SMIELL: In this specific trial.

MR. MARGOLIS: But maybe if you show 001 or maybe K --

MS. SMIELL: Okay.

MR. MARGOLIS: And then people won't argue about it being effective for people --

MS. SMIELL: We can look at 45 -- 43.

MR. MARGOLIS: -- because it was, in this trial.

MR. ROSENBERG: It's no better than placebo.

MR. MARGOLIS: In this trial.

MR. ROSENBERG: In this trial.

MR. MARGOLIS: But in the others it might have been.

MR. McGUIRE: That's correct. The F and the -- the F and the K trials, please.

MS. COELLN: Can we have slide 17?

MR. McGUIRE: Dr. Mustoe?

MR. MUSTOE: Yeah, I would just say that I still find -- I can accept that in your 800 patients you have an aggregate that showed that you have a wound-healing effect. But you can't -- you've got 125 patients in 002 where you were at a 100 microgram dose, and you didn't have an effect. So how can you come back and say that the concentration is critical? I just -- your data doesn't support that, that 100 microgram dose is critical -- that the concentration is critical.

And so I think that gets back to the point that you'd like to have it that the dosing -- that the patient can put on any dose, and it's going to work. And I would say that you haven't -- what you really have to come back, I think, and say, is, the patient has to be extremely careful in how much they put on, or otherwise it's going to be used in an indiscriminate fashion.

MS. SMIELL: Keep in mind what we are requesting is that the layer be the thickness of a dime, which is approximately one millimeter.

MR. McGUIRE: Dr. Lipsky?

MR. LIPSKY: Can we clarify a couple

of things for me, please? One is, as I understand it, the way the patients were instructed during the trials was the thinness or thickness of a dime. So if we're going to be consistent, as we're asking the sponsor to be consistent, shouldn't we ask them to label it the same way they did the study?

MR. EAGLSTEIN: Can I clarify that?

MS. COELLN: I can clarify that. In the first three studies we used a calculation that was designed to deliver a millimeter of thickness, which is why in the 002 Study we used the descriptor "thickness of a dime," since a dime is approximately a millimeter thick.

I also think Dr. Eaglstein had some comments that he wanted to make.

MR. LAVIN: Yeah; can I just ask one more question, which is a pragmatic one? How is this physically put on? Is it put on the finger, and then from the finger to the wound? Or is it -- is the applicator directly touching the wound?

MS. SMIELL: No, the instructions were that there should be either a gloved fingertip, gauze, cotton swab, or a tongue depressor that was used to receive the gel from the tube and then to spread it onto the wound with that.

MR. LAVIN: Well, from an effective control point of view, I'm glad to hear that. Otherwise, you'd have to get into instructing the patients to wash -- or whoever to puts it on, their caregivers, to wash their hands prior to putting it on.

MS. SMIELL: We do that as well.

MR. LAVIN: But if it's going to go on gauze, you're going to use a whole lot more of this product than if it goes on, say, a tongue depressor, which is non-porous.

MR. McGUIRE: Well, we have a -- we have a problem here with the dosing, in that we're trying to -- we're trying to extract some data out of a trial that showed no difference between agent and vehicle. And I don't see how you -- I don't see how you can do that.

Dr. Eaglstein, help us out.

MR. EAGLSTEIN: I don't know if I can help on -- there is the question of "Could there be too much?" And I guess if you feel that the data shows that, maybe the dime, the dime size, the dime-thin layer would still give an end point.

But I did want to mention that actually in dermatology or in topical therapy, we do

find this same thing all the time, like with topical steroids. We don't think it's how much you put on, but how concentrated and how active that molecule is. Or with fluorouracil, we find that one and 5 percent topical had the same effect. I mean, it isn't so different than what we see with the topicals. Antifungals aren't more effective if you put them on thirty times a day. If you see what I'm trying to say, there is --

There is, at least it seems to me, clinical and biologic precedent for the concept that probably what counts is the concentration of the formulation at the interface between the tissue and the material.

MR. McGUIRE: Yeah, Dr. Eaglstein, you and I use the same drugs, and we probably use them very much the same way. My point is that I don't see how we can extract that conclusion from this study, in which --

MS. COELLN: We have data from the case study, if you'd like to see that.

MR. McGUIRE: -- in which there was no separation of vehicle from becaplermin.

MR. EAGLSTEIN: You mean n-02?

MR. McGUIRE: N-02, yeah.

MR. EAGLSTEIN: Right. Didn't you show --

MS. SMIELL: But there were still people who healed, and that's -- those were the people we were showing, the percentages of healed in each of those categories.

We can look at the pivotal trial, which we all agree showed efficacy. And you see again, and this is percent compliance again, that anywhere from 100 compliance all the way through to 1500 percent, or fifteen times prescribed amount, you still see consistent efficacy.

MR. McGUIRE: Dr. Thomas?

MR. THOMAS: I want to do the same -- say the same thing you're saying, but I want to just turn it around. When you specified in your trial that you wanted this put on there the thickness of a dime, this is what you got, a spread all the way across.

MS. SMIELL: This is calculated.

MR. THOMAS: Well, that even makes less sense. If they're trying to calculate it and you're telling me they got fifteen times the dose, then that's all the more reason to put some measure in. What I'm concerned is that in the practical

world people are going to fill up a cavity with this stuff. And I think there should be some description of how much to use.

And I also agree with you that we can't tell whether concentration or amount is important, but that's all the more reason for trying to do some measurement.

MS. SMIELL: Another point about this is, this does not take into account any waste that occurred when they transferred from the tube to the wound. This is a safe product. And I think that being a prescription product, that they may be less likely to want to fill their wound like any other hydrogel.

MR. McGUIRE: Okay.

MS. SMIELL: The other concern we have is the anxiety that may be felt over the appropriate measurement being obtained on any sort of device to measure.

MS. COELLN: And again, we agree that there should be some indication to the patient on how much to apply; hence, the description of the thickness of a dime, 'cause it's something that most people in the United States will be able to visualize.

MR. McGUIRE: Well, this may be -- this may be trivial, but there is -- there is a Silvadene culture out there that fills every available spot with Silvadene, and if they get their hands on this product, they'll just kill it with this.

MR. THOMAS: You can't fill cavities with this stuff.

MR. McGUIRE: I think we're ready for probably the last bit of discussion on this point. How does the -- how does the Advisory Committee vote?

"If becaplermin is approved, should instructions for measure dosage based on ulcer area, as was used in three of the efficacy trials, be recommended in the label?

"Please discuss the possibility that excessive administration of drug might diminish efficacy.

"If becaplermin is approved," and this is the question, "If becaplermin is approved, please discuss whether there should be further post-marketing exploration of drug concentration, amount applied to the ulcer, or other dose-related issues, such as schedule."

What I think I'm -- I hope I'm not leading the Committee, but what I hear -- what I think I'm hearing from the Committee is that you're not satisfied that you have enough data that moves you strictly toward a concentration of microgram per gram in the product, and that you would like to see some label -- some limits or some suggestions on the amount delivered to the ulcer.

MR. F. MILLER: Joe --

MR. McGUIRE: Yes?

MR. F. MILLER: I would just like to make a comment. In this population, many of them are not capable of putting medication on. You know, many of them can't see adequately. And in our part of the world, they -- a lot of them are very obese and, you know, they can't get to the bottom of their foot or to, you know, this part of the anatomy. So that if you don't have something that's very specific, it's probably not going to get on anyway, or maybe not adequately. But if you don't have something very specific, it's even less likely to be efficacious in that regard.

MR. ROSENBERG: Joe, the Aldara is very successful, the little packets, one-time use. And they can be sized for different size ulcers -- I

mean, that type of delivery.

MR. McGUIRE: There are a lot of technical ways to get around this. I don't think -- I don't think that's the issue.

Kurt, this question, this question 4, is really phrased as a discussion, and you've heard a lot of discussion.

MR. STROMBERG: I think if you'll move up to the first question, that is what we seek. You're voting on "If becaplermin is approved, should instruction for measured dosing based on ulcer area, as was used in the three efficacy trials, be recommended in the label?"

MR. McGUIRE: Okay. As I said, I believe what I'm hearing from the Advisory Committee is that there should be some recommendations on the amount delivered on an area basis. All in favor of what I attempted to formulate?

MS. BERGFELD: I'd like to ask a question. I'm not sure that I could vote for that, even though I think there should be a declaration or clarification in the labeling as to how much should go on, but not specific to the size of the ulcer, but to the thin layer that's been advocated by the company.

MR. STROMBERG: The size of the ulcer has been used to --

MS. BERGFELD: I can't hear you.

MR. STROMBERG: The size of the ulcer has been used to determine an amount of gel given.

What is done is to measure length by width, divide by four, run out a ribbon the length of that in centimeters, and then apply that to your wound.

MS. SMIELL: The history of that equation is that -- that length times width, divided by four, was devised so that a thickness of a dime layer, a millimeter layer, will be applied to the wound. We saw that even using that, we get the same amount of variability in the compliance with that, as we did in the "thickness of a dime" descriptive instruction that was given in one study.

MS. COELLN: I'd like to further --

MR. McGUIRE: I think -- I think what I'm hearing from members of the Committee is that "thickness of a dime" means something to you and it means something to me; it may be less meaningful to a patient. And "the length of a ribbon based upon the ulcer area" might be -- might be more limiting.

Dr. Coelln, you had -- you wanted to

help?

MS. COELLN: Yes. What we would like to suggest as perhaps an alternate is that within the labeling we could also include a statement that would be clear that more gel is not necessarily better, or is not better, does not improve the adequacy of the product, so patients will know not to gob this stuff on.

MR. STROMBERG: I think the history of wound healing is replete with imprecise approaches to the problem. I think we compound that if we don't attempt to be as quantitative as possible, and follow the results of the first three trials.

MR. McGUIRE: Dr. Mustoe?

MR. MUSTOE: Yeah, I would just say to the company, perhaps you can come up with a -- I agree that this "length times width divided by four" sounds cumbersome. I would challenge you to come up with either a better delivery system or better method of quantification. But "millimeter," "thickness of a dime," we're saying is not adequate.

MR. LAVIN: Could you just --

MR. STROMBERG: I would have "the length times width," and put in parentheses, "or

approximately the thinness of a dime" for those who -- I mean, it just seems like it gives a simpler definition and gives the same information, according to what the company has found.

MR. McGUIRE: You know, I think what I'm hearing is that people want some limits made on the amount to be delivered, and "thickness of a dime," if you're, you know, in Pennsylvania where it gets dark early and you can't see your feet and it's cold and -- I don't know, I think it just ought to be squeezed out and put on. I don't know.

I think we've spent a lot of time on this. Dr. Wilson?

MR. WILSON: Yeah, I just had a question. What is the theoretical basis for why more might be less effective? I guess I just don't -- is that oxygen deprivation or something? I just don't understand the theoretical basis for why more would be less effective, since we're making such a big deal of this.

MR. McGUIRE: Well, no; I raised it as a -- I raised it as a question because, you know, there are biological examples where an agonist doesn't -- is not an agonist beyond certain concentrations. And Dr. Mustoe cited experience

with cytokines and growth factors.

And I think that's probably not the case here. I think we're -- I think we're attempting to control the amount that's used per ulcer for other reasons. I don't think anyone has the -- has the notion that it's toxic or acting adversely.

MR. WILSON: Well, the way it's stated in the question, the basis for this is because, No. 3, the first three trials used a specific amount based on ulcer size, and then the third one used just the -- the last one used the dime analogy. And that was less efficacious than the first three, so that was the basis of the -- of this question. So I'm implying from that that there was concern by the FDA that the last one, which actually ended up using more drug, was somehow less efficacious. Am I correct?

MR. MARZELLA: That was the observation, that if one looks at the 100 microgram per gram formulation, phenomenologically just looking at numbers, that there is an increase in use, so that by the time that one reaches the 002 Trial, 800 -- 800 percent more drug was used, and there was progressively less efficacy. But that's

-- we're emphasizing also that's just an observation.

And I'd like to echo the fact that given the fact there's so many uncertainties, that it would be appropriate to include instructions on measured dosing, as was done in the three trials where efficacy was demonstrated.

MR. McGUIRE: Tom, I've talked a lot. Would you like to phrase the question? I mean, please will you phrase the question? That's what I mean.

(Laughter.)

MR. MUSTOE: Should the drug dose be measured in a quantifiable fashion, or should there simply be a descriptive term, that it should be applied the thickness of a dime?

MR. McGUIRE: Okay, let's put it in the form of a yes/no, yes/no question. Oh, just all in favor of the former.

MR. MUSTOE: Yeah, all in favor of the former.

MR. McGUIRE: We can have the vote.

MR. HASHIMOTO: What is the former?

MR. McGUIRE: The former is, Ken --

MR. MUSTOE: That it's a -- that it's

a quantifiable measurement, versus a descriptive term of "thickness of a dime."

MR. McGUIRE: "Length of ribbon" somehow related to area of ulcer.

All in favor?

(Members voted.)

Nine. Okay. Nine.

All in favor of using some descriptive technique, "thickness of a dime," pfennig, mark?

MR. ROSENBERG: Has any research been done with small focus groups to see if people can deliver it the thickness of a dime? It's the thing companies do all the time about color of their label or --

MR. McGUIRE: The company's over there. But let's vote on the application based on some other description, "thinness of a dime," for example. Who's in favor of that?

(Members voted.)

Six. Okay.

MR. C. MILLER: At the risk of extending this conversation, I was thinking about -- how about one half of four thirds, pi r2, or t2?

(Laughter.)

MS. COHEN: I'll vote for that.

MR. McGUIRE: Okay. You know, I may just turn this over to you.

Dr. Miller?

MR. F. MILLER: Can I ask one question of the sponsor?

In the studies the patients applied their own medication, did they not? And was that a difficult task? What happened?

MS. SMIELL: We had a mixture. There were some patients that required a caretaker to do that or a nurse to do that. So those who were able, did. These were all outpatients, obviously. And those who could not, just like any other dressing, a caretaker did it.

MR. F. MILLER: Did the caretaker patients overall do better than the self-medicated? You know, overall -- because this would apply to all the care of the ulcer. Do you have that data?

MS. SMIELL: We don't have that data. We didn't collect that information.

MR. F. MILLER: Yeah. That would be interesting to see, because compliance would be a major factor in all aspects of wound care.

MR. McGUIRE: That's a very good

point.

Okay, I'm going to read the last question, which is about a quarter of a page:

"Safety of drug product. Becaplermin is manufactured as a preserved multi-use low bioburden product, with the absence of specifiable objectionable microbes. Several types of data support the microbial safety of this product:

"One, no differential incidence in infection-related adverse events was observed in clinical trials between product, placebo, or standard care arms.

"Two, no bacteria, fungi, or yeast have yet been detected in tubes of the finished product using the microbial limits test. Limit of detection is 10 colony-forming units per gram of gel product.

"Three, the preservative system is bactericidal and fungicidal, and the preservative effectiveness test which challenges the product with individual microbes of 105, each per gram of product. Lower extremity diabetic ulcers are inherently microbially contaminated, and are considered to be in bacterial balance even if they contain up to 105 CFU per gram of wound tissue.

"Becaplermin is not systemically bioavailable. The drug is well tolerated. Theoretical concerns raised by the biology of PDGF -- *i.e.*, increased vascular events or neoplasia" -- "neoplasms have not been observed. Product discontinuations, infectious adverse effects, tumorgenicity, cardiovascular problems, and deaths were similar between standard care, vehicle, and product treatment arms.

"The vehicle alone did not adversely affect healing, but in fact, outperformed standard care. The serious or clinically significant adverse effects have been observed thus far and no" -- that should be "No serious or clinically significantly adverse effects have been observed thus far in subjects treated with becaplermin.

"The question is, considering the information above, does the Committee concur that becaplermin has been adequately demonstrated to be safe for its intended use?"

Discussion?

MR. ROSENBERG: Call the question.

MR. McGUIRE: You mean you don't want to discuss this, Bill?

MR. ROSENBERG: No; I want to vote.

MR. McGUIRE: Okay, let's have the question. Who thinks it's safe?

(Members voted.)

Okay. Ms. Riley is going to read the votes into the record for the transcription. Tracy, just a minute. Okay, it's yours.

MS. RILEY: Okay. A recap on the scores for the record:

Question 2(b), there were eleven yes and four no.

3(a) was deferred to get data on wound location.

3(b) is thirteen yes, two abstain.

4(a), thirteen yes, two abstain.

4(b), nine yes, six no.

And on Question 5, fifteen yes, zero no.

MR. McGUIRE: I'd like to -- I'd like to thank the audience for your patience.

And is there word from the Agency?

MS. WEISS: I very much appreciate all the helpful advice and discussion that we had today.

We didn't really follow up with Question 4(b), which was basically should further

exploration be done in post-marketing. Is that -- is it reasonable to assume that that is something we should be discussing?

MR. McGUIRE: That was implied, yeah.

MS. WEISS: And the second thing, which will be very quick: there was a lot of discussion earlier on about concerns about the fact that there may be a lot of use in hands other than experts hands, such as we'd seen with Dr. Steed in his studies. Would -- should the labeling -- and we've had experience doing this before with other types of products, such as antineoplastic products.

Would it be adequate for the Committee, for labeling, to recommend that this type of product be used with people experienced in wound care, or people such as dermatologists and vascular surgeons, some warning to that effect in the labeling? Is that what the Committee thinks would be useful to try to help ensure that this is going to be used in the appropriate hands?

MR. McGUIRE: I don't think issues of risk were brought up today.

MS. WEISS: Not risk, but just optimization of -- optimization of the healing, or use of this product for best efficacy.

MS. COHEN: Are you saying that the consumer would be unable to do it after you --

MS. WEISS: No; in terms of -- in terms of prescribing, in terms of person who's -- a person who's prescribing the medication, I think is the question, in terms of the issues like the things we talked to you before, the proper debridement, infection control, assessment of the wound.

MR. McGUIRE: It sounds to me like the indications are going to be very narrowly defined, from what we've heard today.

MS. COHEN: This isn't an OTC drug, so I don't understand your question.

MR. McGUIRE: Mrs. Cohen, I missed it.

MS. COHEN: I missed it too, but I think it's just been explained. You mean the specialty of the physician? Is that what you're saying?

MS. WEISS: Yes.

MS. COHEN: Lots of luck.

MR. McGUIRE: Okay. Well, Mrs. Cohen had the last word.

Thanks again for your participation. It's been a big meeting. And we'll see each other

at 8:30 tomorrow morning.

(Whereupon, at 4:14 p.m. the meeting was adjourned.)